Hormonal Therapy for Male Sexual Dysfunction

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EDITED BY

Mario Maggi
Director, Sexual Medicine & Andrology
University of Florence
Florence, Italy

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Editorial Offices
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The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Preface

The sexual lexicon is based on messages continuously exchanged among individuals, which can be rephrased and read under various perspectives. The capacity of exchange in sexual messages within the body is made possible largely by two different mechanisms: the nervous system, which transmits electrochemical signals as two-way traffic between brain and peripheral tissues or between tissues in reflex circuits; and the endocrine system, which releases chemical mediators termed hormones into the circulation for action away from their original sites. Hence, the endocrine system is an integral part of the sexual lexicon. However, only receptive individuals know the language and can read the message. Hormones are messages written in a biological language that can be easily read by receptive cells (those expressing the cognate receptor). Sexual hormones allow communication among lover's cells, because, even though hormones and receptors are physically distinct structures, they ultimately perform the same function.

Male sexual disorders often derive from a local or generalized misunderstanding of sexual messages. A better understanding of how hormones work and communicate will lead to the discovery of effective therapies to improve sexual communication. This book will provide the rationale for hormonal therapy in male sexual disorders, explaining the language of sexual endocrinology and helping to rephrase it when necessary.

Endocrinology has traditionally been defined as a branch of biological science that concerns itself with the actions of hormones and the organs in which the hormones are produced. Sexual hormones not only regulate gametogenesis, but also control the dimorphic anatomical, functional, and behavioral development of males and females that is essential for sexual functioning. It is of particular interest in this regard that no exclusive male or female sexual hormones have been identified. All hormones characterized to date are present in both sexes, and both sexes have receptor mechanisms that allow responses to all hormones. Sexual dimorphism is the result of differences in the amounts of individual hormones and differences in their patterns of secretion, rather than their presence or absence. It follows that sexual endocrinology requires a precise genetic programming that allows for the synthesis of an appropriate enzyme complement in the ovary or testis, which in turn catalyzes the formation of the appropriate amounts of hormones during the critical stages of life. The endocrinological control of sexual activity encompasses every phase of the process, including many behavioral aspects.

Sexual hormones might have multiple effects. An example of such a hormone is testosterone. Some of its diverse actions include fusion of the labioscrotal fold in the male embryo during embryogenesis, induction of male differentiation of the Wolffian ducts, regression of the embryonic breast (in some species), growth of the male urogenital tract, induction of spermatogenesis, growth of beard and body hair, promotion of muscle growth, retention of nitrogen, increased synthesis of erythropoietin, temporal regression of scalp hair, hyperplasia of the sebaceous gland with increased sebum production, development of prostatic

hyperplasia in aging males of several species, secretion of the ejaculate, and virilization of the male external genitalia (including penis), along with discrete hypothalamic nuclei. It was originally believed that androgens exerted these diverse effects by distinct mechanisms. However, one of the most important findings from genetic studies and from modern molecular biology is that diverge effects can be modulated by a single mechanism: the androgen receptor.

So, at the end of the day, sexual endocrinology is an important part of sexual medicine: read this book faithfully!

Mario Maggi, MD
University of Florence
November 2011

Contributors

Elisabetta Baldi
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Elisa Bandini
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Cesare Carani
Endocrinology Unit
Integrated Department of Medicine,
Endocrinology, Metabolism and Geriatrics
University of Modena and Reggio Emilia
Baggiovara (Modena), Italy

Helen Casale
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Alessandro Cellerino
Scuola Normale Superiore and
Institute of Neuroscience – CNR
Pisa, Italy

Silvia Cerpolini
Interdepartmental Centre for Sexual Health
Protection (CISS)
University of Bologna
S. Orsola Hospital
Bologna, Italy

Peggy T. Cohen-Kettenis
Department of Medical Psychology
Center of Expertise on Gender Dysphoria
Neuroscience Campus Amsterdam
VU University Medical Center
Amsterdam, The Netherlands

Antonietta Costantino
Interdepartmental Centre for Sexual Health
Protection (CISS)
University of Bologna, S. Orsola Hospital
Bologna, Italy

Giovanni Corona
Endocrinology Unit, Medical Department
Azienda Usl Bologna
Maggiore-Bellaria Hospital
Bologna, Italy.
and
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Alessandra D. Fisher
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Gianni Forti
Endocrinology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Mauro Gacci
Department of Urology
University of Florence
Florence, Italy

Antonio R. Granata
Endocrinology Unit
Integrated Department of Medicine,
Endocrinology, Metabolism and Geriatrics
Azienda USL Modena
Nuovo Ospedale Civile S. Agostino Estense
Hospital
Baggiovara (Modena), Italy

Emmanuele A. Jannini
School of Sexology
Department of Experimental Medicine
Universi ty of L'Aquila
L'Aquila, Italy

Baudewijntje P.C. Kreukels
Department of Medical Psychology
Center of Expertise on Gender Dysphoria
Neuroscience Campus Amsterdam
VU University Medical Center
Amsterdam, The Netherlands

Andrea Lenzi
Department of Experimental Medicine
University of Rome "La Sapienza"
Rome, Italy

Andrea Mazzatenta
Faculty of Psychology
G. d' Annunzio Chieti-Pescara University
Chieti, Italy
and
Faculty of Veterinary Medicine
Teramo University
Teramo, Italy

Diego Mazzatenta
Centre of Surgery for Pituitary Tumors
and Endoscopic Skull-based Surgery
Bellaria Hospital
Bologna, Italy

Maria Cristina Meriggiola
Interdepartmental Centre for Sexual Health
Protection (CISS)
University of Bologna, S. Orsola Hospital
Bologna, Italy

Annamaria Morelli
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Valeria Pugni
Endocrinology Unit
Integrated Department of Medicine,
Endocrinology, Metabolism and Geriatrics
University of Modena and Reggio Emilia
Baggiovara (Modena), Italy

Vincenzo Rochira
Endocrinology Unit
Integrated Department of Medicine,
Endocrinology, Metabolism and Geriatrics
University of Modena and Reggio Emilia
Baggiovara (Modena), Italy

Linda Vignozzi
Sexual Medicine and Andrology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

Lucia Zirilli
Endocrinology Unit
Integrated Department of Medicine,
Endocrinology, Metabolism and Geriatrics
University of Modena and Reggio Emilia
Baggiovara (Modena), Italy

1

Male Gender Identity and Masculine Behavior: the Role of Sex Hormones in Brain Development

Baudewijntje PC Kreukels and Peggy T Cohen-Kettenis

VU University Medical Center, Amsterdam, The Netherlands

Typical male gender development

Prenatal sexual differentiation

Sexual differentiation is a stepwise process starting with a difference of the sex chromosomes (XX for females, XY for males). The embryo starts off with two basic pairs of reproductive structures, the Müllerian ducts and the Wolffian ducts. A gene located on the Y chromosome (SRY) induces the development of the testis. A few weeks after conception, the testes will start to produce testosterone and Müller Inhibiting Substance (MIS). These hormones of the testes direct male development. The Wolffian ducts develop into male internal reproductive organs, and the MIS, produced by the Sertoli cells of the developing testes, causes the Müllerian ducts to regress. In the absence of a Y chromosome (and therefore testes and androgens), ovaries will develop. The Wolffian ducts will regress and the internal sex organs will develop along the female line, the default route. The external genitals also develop from identical structures. In males, testosterone and its derivative dihydrotestosterone (DHT) direct the genital tubercle to become the penis and the genital swellings fuse to form the scrotum, whereas in females, in the absence of testosterone, these structures become a clitoris and a labia.

Apart from the sexual differentiation of the genitalia, sex hormones in the prenatal environment influence the differentiation of the brain into male or female. Pre- and early neonatal exposure of the brain to sex hormones leads to permanent changes in the nervous system. These effects are referred to as organizational effects. From vertebrate models we learn that the steroid hormone testosterone accounts for the majority of the known sex differences in neural structure and behavior. In lower animals, the presence or absence of testosterone at the time of a critical period of brain sexual differentiation influences the morphology of certain brain nuclei. Like its influence on the development of the genitalia, the presence of testosterone leads to male sexual differentiation of the brain and results in male-typical behavior, while a

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female brain and female-typical behavior are found to be the outcome of the absence of testosterone. When the testes are formed, they begin to produce testosterone and from this moment on there is a sex difference in testosterone concentrations between male and female fetuses. Through its effects on neurogenesis, cell migration, cell death, and the differentiation of neural circuits, testosterone has its effects on neuronal organization.

Influence of prenatal hormones on male gender development in humans: evidence from non-clinical samples

Gonadal hormones are also thought to influence the sexual differentiation of brain and behavior in humans, but the exact mechanisms and timing remain unclear. Early in life, sex differences are observed in play behavior and preferences. An approach to study the effects of prenatal testosterone on gender development is to relate hormonal levels in maternal serum or amniotic fluid to variations in subsequent gender-related (play) behavior in non-clinical samples. Maternal testosterone predicted the amount of male-typical behavior in daughters, as measured by parent questionnaires. Amniotic testosterone was found to be related to male-typical play behavior, as assessed by maternal reports of childhood sex-typed activities in male as well as female offspring. However, other studies did not find support for the hypothesized relationship between prenatal testosterone exposure and postnatal gender-related play behavior.

A frequently studied indirect measure of prenatal exposure to sex hormones is the ratio of the length of the second digit (2D, index finger) to the length of the fourth digit (4D, ring finger). The ratio is lower in men than in women and is assumed to be affected by exposure to prenatal androgens. Normal polymorphisms in the androgen receptor (AR) gene are reported to correlate with digit ratios in men. Using 2D:4D as a marker, prenatal androgen exposure has been found to be associated with behavior more commonly displayed by men than women and to be related to aggression, risk-taking, and disorders more common in men such as ADHD and autism.

Another research paradigm to study the influence of prenatal brain exposure to sex hormones comes from the study of opposite- vs, same-sex twin pairs. It is assumed that fetal androgens may be transferred from the male to the female fetus and that the female twin might thus be androgenized by her male co-twin. However, results of such studies have been found to be inconsistent.

Early cognitive gender development

From cognitive developmental studies we know that learning about being a boy or a girl starts in infancy. Babies as young as 9 months are already able to visually discriminate between the sexes. The ability to verbally label the sexes comes later, at around 28 months. As toddlers are often hardly aware of genital differences, they use hairstyle and clothing as a criterion for classification.

With regard to the concept of gender, children first learn to identify their own and others' sex (*gender labeling*). Next, they learn that gender is stable over time (*gender stability*). Finally, they learn that superficial changes in appearance or activities (a boy does not become a girl overnight if he puts on a wig or plays with Barbie dolls) does not change one's gender. This is the last stage of gender constancy (*gender consistency*). This last phase is reached between 5–7 years, but long before that age, children appear to have knowledge about gender stereotypes (for an overview see Ruble *et al.* 2006). For instance, 3-year-old children, who saw videotaped infants labeled male, rated these infants as "big," "mad," "fast," "strong," "loud," "smart," and "hard." When labeled female, they were rated as "small," "scared," "slow," "weak," "quiet," "dumb," and "soft". Three-year-olds also believe that "boys hit people." Gender stereotype knowledge increases rapidly after 3 years of age and appears to develop throughout childhood. Once established,

gender stereotypes influence the way new information is processed. Children remember stereotype consistent information better than inconsistent information, and even distort inconsistent information. For instance, when a picture is shown to them of a woman flying an airplane, they may either report having seen a man flying the airplane or a woman doing something else, such as cooking.

According to some cognitively oriented theorists, children need only basic information rather than extensive knowledge about gender to further develop gender role behavior. For instance, children prefer same-sex toys, imitate same-sex models, and reward peers for gender-appropriate behavior before they reach complete gender constancy. Therefore, a complete understanding of gender is perhaps not important in the very early stages of gender development.

Gender development is a process that not only involves cognitive aspects but also involves affective meanings. As soon as a child identifies with one of the sexes, these values will affect their self-perception and self-concept. For instance, boys are usually proud of being a boy and look somewhat down on girls.

Gender segregation

At very early ages children become interested in same-sex playmates. Boys like other boys better than girls and spend a fair amount of time in the company of other boys. Changing this peer preference appears to be difficult.

Children thus spend an important part of their time in all-male or all-female groups. Boys tend to play in larger groups, play in more public places and with less proximity to adults, and play rougher and with more body contact. Boys fight more and their social interaction is oriented more toward issues of dominance. Girls' groups are less hierarchically organized and their friendships are more intense. Girls appear to use language to create and maintain relationships, to criticize others in acceptable ways, and to interpret accurately the speech of other girls. In boys, speech is used to attract and maintain an audience, to assert one's position of dominance, and to assert oneself when others have the floor. So gender segregation has far-reaching consequences for children's social development and friendships.

The influence of the environment on gender development

Children also learn about gender by observation of role models and by differential treatment. This differential treatment may be more or less direct (e.g. playing different games with boys than with girls) or be more subtle or indirect (e.g. blue and pink clothing). An immense body of literature supports the notion that parents, other adults, teachers, peers, and the media are gender-socializing agents. For instance, mothers talk more to daughters than to sons, teachers praise and criticize boys more than girls, and peers reinforce same-sex and punish cross-sex behavior. In experiments in which the actual sex of an infant is unknown, adults even interact differently with children labeled as boys than with children labeled as girls.

Adults and children are not just influencing gender development by their reinforcement of behaviors. As role models, parents and peers also shape children's gender attitudes and behaviors. Furthermore, gender development seems to be strongly influenced by the media. This was nicely illustrated by an older study among children living in a Canadian town unable to receive television. Before television was introduced, they were less traditional than a control group. Two years later their attitudes had changed dramatically in the more traditional direction.

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Besides biological factors, such as prenatal exposure to testosterone, environmental and psychological factors also play a role in male gender development.

Gender development: sex hormones and the brain after puberty

Later in life, neural circuits and behavioral patterns are activated by changing levels of sex hormones. An example of these so-called activating effects is the stimulation of the already sexually differentiated nervous system by gonadal hormones during puberty. Because steroid-dependent organization of brain and behavior also takes place during adolescence, it has been suggested that these activating effects should also be characterized as organizational effects. The timeframe for organizational effects may not be limited to prenatal and early neonatal periods, but may also include puberty and adolescence. Steroid dependent organization during puberty implies that certain adult sex-typical behaviors are expressed because pubertal hormones first have organized neural circuits in the developing adolescent brain and that these circuits are subsequently activated by gonadal hormones. One example of structural changes that may be the result of pubertal hormone changes is the white matter volume. This increases faster and reaches a bigger overall volume in boys than in girls during puberty and it is thought that white matter volume might be related to the activity of the AR. With regard to brain tissue in adulthood, sexual dimorphism is found for gray and white matter, but the white matter difference is more pronounced, with men having larger white matter volumes than women. Regionally, larger volumes of gray matter are detected in women than in men.

Other sex differences in brain and behavior in adulthood may also be related to the effects of sex hormones. Subcortically, in the hypothalamus, sex differences are observed in the interstitial nuclei of the anterior hypothalamus (INAH-1, INAH-2, INAH-3) and the central portion of the bed nucleus of the stria terminalis, with larger volumes in men than in women. These sex differences in the hypothalamus are thought to underlie sex differences in gender identity, reproduction, and sexual orientation.

Gender-related cognitive functioning has been related to size and shape of the corpus callosum. Sex differences have been reported for the corpus callosum, but there is disagreement about the direction of the sex effect and some studies failed to detect such an effect. Men do show more morphological asymmetry than women and appear to have a somewhat more lateralized brain with left hemisphere dominance for language processing and right hemisphere dominance for spatial processing.

Regions with developmentally high densities of estrogen and ARs show greater sexual dimorphism. For example, the amygdala has a larger volume in males. Sex differences in the amygdala's response have been mentioned as factors to explain sex differences in the prevalence of psychiatric disorders. For instance, depression is less common in men than in women and is associated with sex differences in the role of the amygdala in emotional memory.

Men and women also differ in the occurrence of other psychiatric disorders. Schizophrenia, attention deficit hyperactivity disorder, and autism primarily hamper men (for an overview see Bao & Swaab 2010), whereas eating- and anxiety disorders are more prevalent in women. Sex ratios for neurological disorders differ as well, with Rett syndrome (non-existent in men) and Kleine-Levin syndrome (non-existent in women) as extremes. Finally, personality characteristics also show sex differences. In general, physical aggression appears to be higher in men, whereas empathy has been found to be higher in women.

Genetic studies

Independent of the role of hormones, other biological factors, such as genes, may also influence gender development. Even before the production of gonadal hormones, genes may directly affect brain sexual differentiation. Evidence for the role of genetic factors in sex differences in behavioral traits has been found for play behavior and

aggression. For a review of the evidence for direct genetic effects on sex differences in brain and behavior we refer to Ngun *et al.* 2011.

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Gender identity: a persons' sense of self as being male or female.
Gender role: behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as more typical of the male or female social role.
Disorders of Sex Development (*DSD*) (previously referred to as intersex conditions): congenital conditions in which the development of chromosomal, gonadal, and/or anatomical sex are not entirely male or female.
Gender dysphoria: is the distress resulting from conflicting gender identity and gender of assignment.
Transsexualism or gender identity disorder: extreme end of the spectrum of gender dysphoric conditions, usually characterized by a pursuit of sex reassignment.

A typical development of gender identity and gender role behavior

Research on factors that influence typical gender development generally focuses on gender role or gender related behavior. We have already seen that in non-clinical groups, prenatal exposure to higher levels of androgens may lead to more masculine behavior. Because gender identity usually develops in accordance with an uneventful sexual differentiation, it is difficult to study factors that may influence gender identity development in typically developing individuals. However, studies in individuals with atypical prenatal hormonal levels or individuals that have a gender identity that is not in accordance with their natal sex could help in elucidating the mechanisms underlying gender identity development. Three groups are of interest: children of mothers who took medication during their pregnancies that might have influenced their children's gender development, individuals with disorders of sex development, and transgender individuals.

Intoxications during pregnancy

Daughters of mothers who took diethylstilbestrol (DES), a synthetic estrogen that masculinizes and defeminizes brains and behavior in female rodents, have been found to show higher rates of homosexual imagery or homosexuality than controls, but no masculine gender identity. Effects of exogenous hormones on male behavior and interests are less clear and often conflicting.

In a study among, adults who had prenatally been exposed to phenobarbital- and phenytoin, known to influence sex steroid metabolism, it was found that the individuals as a group did not differ with respect to gender role behavior, but that higher numbers of prenatally exposed subjects reported current or past gender variant behavior and/or gender dysphoria. Gender dysphoria is the distress resulting from conflicting gender identity and gender of assignment. In a group of 147 subjects, there were also 3 transsexuals. This is a remarkably high rate given the rarity of transsexualism.

Disorders of Sex Development (DSD)

Gender development in individuals with CAH

Congenital adrenal hyperplasia (CAH) exposes female fetuses to elevated testosterone levels. This condition is extensively studied to infer the relationship between prenatal hormones and postnatal gender development. These women, who are born with more or less virilized external genitalia, are generally treated early in life to normalize hormone levels and often undergo surgery to feminize

their genitalia. Girls with CAH generally show increased male-typical play behavior. Masculine gender role behavior also appears to be common in women with CAH across the lifespan. In women with CAH, a dose-response correlation has been found; with the more seriously affected "salt-losing" women showing more masculine behavior than the less affected "simple-virilizing" women.

In contrast, women with CAH, who were raised as females, mostly have feminine gender identities. However, these women show a less strong female identification, elevated levels of gender discomfort, and even gender dysphoria (~5%) than non-DSD women.

Gender development and 5α-reductase-2 deficiency (5α-RD-2) and 17β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3)

Children with 5α-RD-2 have an enzyme defect that prenatally blocks the conversion of testosterone into dihydrotestosterone. Consequently they are born with external genitals that are female in appearance. They are usually raised as girls and seem to have a female gender identity, but, if the condition is not discovered in childhood, these children develop male sex characteristics in puberty: growth of their "clitoris" and scrotum, lowering of the voice, beard growth, masculine muscle development, and masculine body fat distribution. After puberty, many of these youngsters start living as males and develop a sexual attraction toward females. These transitions have been primarily documented in non-Western cultures. When raised as boys, these children have a male identity and behave like boys.

Another condition affecting testosterone biosynthesis, which might lead to impaired virilization in male infants, but excessive virilization when these children become adolescents, is 17 β-HSD-3. Gender transitions in 46,XY children with 17β-HSD-3 raised as girls have also been reported. However, such changes did not happen in all affected individuals. De Vries and colleagues (2007) reviewed the literature on gender identity outcome and DSD and found that 59% of the female-raised 5α- RD-2 individuals (69 of 117), and 39% of the 17β-HSD-3 individuals (20 of 51), all above age 12, had gender dysphoria to the extent that they chose to live as males later in life.

Gender development and CAIS/PAIS

Individuals with complete androgen insensitivity syndrome (CAIS), who are raised as girls, are described as very feminine in their gender role behavior, although there may be more variability in their behavior than has long been assumed. They have a female gender identity and in the review by de Vries *et al.* (2007), none of the women with CAIS reported suffering from gender dysphoria or made a gender transition. But in the partial form of this condition, partial androgen insensitivity syndrome (PAIS), another picture emerges. In female-raised individuals, 11% were gender dysphoric or changed gender (5 of 46). In the male-raised group, this percentage was even higher, where 14% were gender dysphoric or changed gender (5 of 35).

Gender development and ablatio penis

A famous case of male identical twins is illustrative in this nature/nurture debate as well. One of the boys lost his penis due to a circumcision accident. The parents were advised to re-assign the child to the female gender and raise him as a girl. Early reports showed that, in contrast to the twin brother, the reassigned child seemed to develop as a "real girl," despite the fact that she had many tomboyish traits. Later, the boy became increasingly unhappy as a girl, and as an adolescent he reassumed the male role. He married and became the stepfather of children. The easily drawn conclusion from this case, that prenatal hormones determine gender identity, seems to be premature, however. In a review reporting on 6 more cases of ablatio penis, the majority lived as females without gender dysphoria.

CAUTION

Male gender role behavior in female-raised children should not be mistaken for a male gender identity.

Concluding remarks

Many parents of children with DSD are concerned about their gender. Some parents are ignorant about the sex of their child for some time. Children with DSD may be ill at birth and may need medical interventions. In addition, the conditions that have been studied vary widely. Levels of prenatal hormones, and timing and duration of the exposure differ between conditions or between individuals with similar conditions and are usually unknown. Therefore, extrapolating the above findings, on atypical gender role development to normal development, has obvious limitations. It is clear from the results of studies of DSD individuals, that a distinction between gender-*role behavior* and gender *identity* has to be made. These study results support the aforementioned findings in non-clinical samples, indicating a relationship between prenatal androgenization and masculine *behavior*. Whether and to what extent prenatal androgen brain exposure results in a male gender *identity* is less clear.

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Prenatal testosterone appears to influence the development of masculine gender role behavior more than the development of a male gender identity.

Transsexuals

Transsexuals have a gender identity that is inconsistent with their natal sex and strongly desire to live in accordance with their gender identity. A complete cross-gender identity may be present from very early ages on. Parents often report that their sons never showed male-typical behavior. Why such young boys identify with girls and want to behave like girls is still an enigma. A supposed discrepancy between genital differentiation on the one hand and hormone induced brain sexual differentiation on the other has been invoked as an explanation for the phenomenon. Because it is impossible to determine prenatal hormone levels in adulthood, post-mortem brain studies, cognitive, handedness and imaging studies are employed to investigate whether the brains of transsexuals resemble those of their natal sex or of their gender identity.

Post-mortem studies

Postmortem studies into the brain material of transsexuals revealed a sex reversal in volume and neuron number in the central portion of the bed nucleus of the stria terminalis and the interstitial nucleus 3 of the anterior hypothalamus in male-to-female transsexuals (MtFs) and a female-to-male (FtM) transsexual. Because all subjects had received hormone therapy, it remains unclear if the differences should be ascribed to this treatment. However, non-transsexual males, who had taken estrogens for medical reasons, did not show a smaller central portion of the bed nucleus of the stria terminalis.

Luteinizing hormone (LH) regulation

Based on the assumption that neuroendocrine regulation of LH is a reliable indicator of the sexual differentiation of the brain, it was postulated that MtFs, like females, would show a rise in LH levels after estrogen stimulation (estrogen positive feedback effect) as a consequence of prenatal exposure to imbalanced sex steroid levels. The opposite was expected to occur in FtMs. However, studies with thorough methodology found no support for a sex reversal in the neuroendocrine regulation of LH in transsexuals.

Cognitive studies

A relationship between prenatal hormonal influences, on the one hand, and sexual differentiation of the brain on the other hand, might be reflected in sex-related cognitive abilities and functional cerebral asymmetry. If a cross-gender identity is (partially) determined by prenatal brain exposure to unusual sex hormone levels, one would expect that transsexuals would resemble their desired sex more than their sex of birth with regard to sex-related cognitive abilities. FtMs would have more male-typical outcomes and MtFs more female-typical outcomes.

In studies examining IQ and verbal/spatial subtests, some samples of individuals with gender identity disorder (GID) show a pattern of cognitive functioning that is not in line with the natal sex. However, the results are too inconsistent to draw definite conclusions. Moreover, the IQ scales are not developed to measure constructs that show large sex differences. Therefore attempts have been made to compare transsexual and non-transsexual samples with other instruments. To reliably study organizing effects of sex hormones on cognitive functioning, one should study untreated transsexuals, that is before any hormonal treatment and surgical steps. In this way differences between transsexuals and controls sharing their natal sex cannot be attributed to the treatment.

Only a few studies examined these constructs in untreated transsexuals. Female patterns of cognitive functioning and functional cerebral asymmetry in MtFs were reported. MtFs showed less functional cerebral asymmetry when processing auditory verbal stimuli and they performed better on a verbal memory test than male controls. In addition, the predicted pattern of gender-atypical cognitive functioning on a verbal memory test was found in FtMs. In another study, untreated MtFs and FtMs scored between male and female controls on male and female favoring tasks. However, still others found a cognitive pattern in untreated individuals with GID that was consistent with that of their natal sex.

Handedness studies

Whether handedness differs between individuals with a GID diagnosis and controls has been investigated both in children and adults. In these studies, the assumption was that prenatal hormone brain exposure explained both the GID and the non-right-handedness. More left-handedness was indeed found in boys with GID than in a clinical control group and in 3 population studies of non-referred boys. Elevated percentages of non-right-handedness in adult MtFs and FtMs were also found.

Imaging studies

Nowadays, imaging techniques are used to investigate whether there is a sex reversal in structure or in functioning of the brains of transsexuals. Diffusion Tensor Imaging is a technique to display the white matter microstructure pattern. Untreated FtMs show a white matter microstructure pattern that resembles their gender identity more closely than their natal sex, and the pattern of untreated MtFs falls in between that of men and women. Magnetic Resonance Imaging (MRI) in untreated MtFs shows that their gray matter volumes are mostly consistent with men (their natal sex), but that the gray matter volume of the putamen was feminized. In addition, cerebral activation patterns in transsexuals prior to treatment seem to share more features with those of the experienced gender than those of their natal sex. This was observed using Positron Emission Tomography (PET) during the processing of pheromones and using functional MRI while viewing erotic film excerpts. Finally, differences have been found within the cortical network engaged in mental rotation between MtFs (prior to as well as during hormonal treatment) and control males. Also, a study in transsexuals under cross-sex hormone

treatment showed a difference in parietal activation during mental rotation between MtFs and control men, which might also be a result of *a priori* differences between the MtFs and those sharing their natal sex (male controls).

Summary and conclusion

From studies in both clinical and non-clinical samples, it seems safe to infer that prenatal exposure to androgens influence certain male gender role behaviors. Not only 46,XY but also 46,XX individuals who are exposed to high levels of testosterone, exhibit behaviors that are typically attributed to males. With regard to gender identity, we cannot draw similar conclusions with the same level of confidence. Elevated percentages of gender dysphoria have been found in 46,XX individuals with known exposure to atypical levels of androgens, but there is not a one-to-one relationship between such exposure and gender identity problems. Also, in individuals with a gender identity that does not correspond to their natal sex, there are indications of exposure to atypical levels of sex hormones. However, these results again do not point to a one-to-one relationship between gender identity and prenatal sex hormone levels. With regard to male development, it seems likely, on the basis of the current evidence, that sex hormones, androgens in particular, lay important groundwork for gender development. Prenatal androgens result in male-appearing genitals at birth. As a result, the environment will consider the child as a boy and treat him likewise. Prenatal brain exposure to androgens also results in various male-typical behaviors. The developing boy will consider (male genitals) and label himself (cognitive development) as a boy, choose male models and increasingly create his own social environment. If all these factors (body/genitals, perception of the environment, self-perception, behaviors, and preferences) work in accordance with each other and reinforce each other, there seems to be no other possible outcome in adulthood than a firmly established male gender identity and corresponding male behavior patterns, including sexuality. However, when some of these elements work for some reason against a male pathway, it is likely that the adult will have a gender variant identity and/or show gender variant behaviors and preferences.

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2

Pheromonal Regulation of Male Sexuality

Andrea Mazzatenta[1], Diego Mazzatenta[2], and Alessandro Cellerino[3]

[1] University of Teramo and University Chieti-Pescara, Teramo and Chieti, Italy

[2] Bellaria Hospital, Bologna, Italy

[3] Institute of Neuroscience, CNR, Pisa, Italy

Chemosexual behavior is based on the releasing and receiving of biochemical signals, both within the body and between individuals. In 1932, the concept of communication mediated by two groups of chemical compounds, known as endo-hormones and ecto-hormones, was introduced. The endo-hormones, or hormones, act within the body, while the ecto-hormones leave the body to be received by another individual, where they can regulate physiology and behavior. The pheromones are a class of ecto-hormones that are exchanged only between individuals of the same species, and among these are the sexual pheromones that elicit sexual and reproductive behavior. From a biological point of view, male sexual disorders indicate the need to investigate faults in chemosexual communication, most of which are related to hormones, although the pheromonal messages also need to be taken into account. A better understanding of how pheromones behave in their activation, regulation, and modulation of the hypothalamus, and of the hormonal cascade that they can induce, will help therapies to be defined for the recovery of chemosexual communication. This chapter will focus on initial sexual communication events that are mediated via pheromones across sexual partners, and these include pheromonal communication, pheromone stimuli, the pheromone-releasing system, the pheromone-sensing system, pheromone neurobiological-physiological effects, pheromonal pathology, and pheromonal treatment.

CAUTION 1

Human sexual pheromones are steroid-derived compounds that can be harmful if not correctly treated and administered.

Pheromonal communication

Communication is an essential social behavior in animals, and this behavior is consummated in a number of forms that are related to the sensory repertoire of any given species. In general, language is mistakenly accepted as the only communication system in our species. However, humans express a wide range of non-verbal behavior, which includes chemosexual communication. Pheromone cues can carry information about

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sexual and social status, for example gender, maturation level, reproductive status, individual identity, consanguinity, health status, dominance, ownership, and competitive ability, and they can have important influences on adaptive and evolutive processes. Chemical signals are the major exchanges, and dominate our sociosexual interactions. Pheromonal communication is based on information processing, which occurs in the limbic system without any cognitive, conscious assessment. Pheromonal communication produces sexual selection due to differential access to mates through intrasexual selection and intersexual selection.

Intrasexual selection results from the differential ability to compete against same-sex rivals, while intersexual selection results from the differential ability to appeal to the mate preferences of the opposite sex. Fitness benefits obtained through sexual selection of men have been described according to two theories: as the good-genes, and the good-provider. In both theories, increases in fitness are investigated according to the female choices that recog-nize the genetic indicators or material benefits in males that will be passed on to the offspring, or will help in their survival, thereby also increasing the female's inclusive fitness and personal survival. Both theories can be applied to the biology of human sexual selection, where the material benefits are easy to identify, while the genetic indicators are not. However, the sexual selection of genetic traits is restricted to biological processes only, while political, social, ethnic, and ethical viewpoints are excluded and are incorrect. Pheromones are direct expressions of genetic sexual selection that might have operated ancestrally in human evolution. These cues elicit neuronal, endocrine, physiological, and behavioral modifications, and indicate how important and complex pheromonal communication is in human sexual selection.

The main questions that arise regarding the principal steps of sexual behavior are:

(i) What is the role of pheromones in mate selection?
(ii) How do pheromones drive sexual behavior?
(iii) Are pheromones involved in fecundation?

Up to about the last decade, the answers to these questions were: fate or causality. Conversely, recent studies have shed light on the crucial biological events that underlie this sexual selection and its evolution.

The answer to the first of these questions is intrinsic to the biological principles that regulate behavior in the search for a partner of the same species and the opposite sex. These provide the distinctive characteristics of sex, maturation level, reproductive status, gender, individual identity, consanguinity, and health status that belong to the good-genes theory, and the social, dominance, ownership, and competitive abilities that belong to the good-provider theory, which all result in species fitness. Pheromonal signals carry this information all together, while other sensorial indicators are not so exhaustive.

In mammals, such as humans, a broad repertoire of glands (e.g. perianal, preputial, arm-tip, harderian, brachial, and skin glands, to name but a few) and released body fluids are involved in carrying chemical information. Urine, for example, is a source of an amazing variety of chemosignals, and its composition can be constitutive or inducible: for hormonal cycling, maturation stage, co-specific signals, and other factors. These signals are responsible for the dramatic physiological regulation and behaviors, discovered in mice, known as the Bruce, Lee-Boot, Whitten, and Vanderbergh effects. In the Bruce effect, the resulting behavior is the abortion of a pregnant female, with the female physiological regulation induced by a male pheromone that is secreted in the urine that is different from the pheromone of the sire-male of the pregnancy. This behavior results in a new female heat period and copula with

the new male, ensuring higher offspring fitness. In the Lee-Boot effect, the resulting behavior in females living together in the same cage is the progressive suppression of the cycle, with the female physiological regulation induced by a female pheromone secreted in the urine. In the Whitten effect, the resulting behavior in females living together in the same cage where a male is introduced is cycle synchronization, or indeed restart if they were under the Lee-Boot effect, with the female physiological regulation induced by a male pheromone secreted in the urine. In the Vanderbergh effect, the resulting behavior is the acceleration of the onset of puberty in a female exposed to a mature male who is not the father, with the female physiological regulation induced by a male pheromone secreted in the urine. In humans, at least two of these specific effects have been demonstrated: acceleration of the onset of puberty in female teenagers when exposed to a stepfather; and cycle synchronization in woman with shared environments, such as living together, in college, at work, in prisons, etc.

Urine and sweat secretions are the sources of another set of unusual behavioral-physiological signals: the major histocompatibility complex (MHC) component. The MHC is a source of unique individual signals that can influence individual recognition, mating preference, and regulation of social behavior in human and mammals. The individual pheromonal identity, through the signaler pheromone (see section on pheromone stimuli), is decisive in sexual and reproductive behavior for genetic identification, to avoid consanguinity. It has been demonstrated that male mice display mating preferences for oestrous females with dissimilar MHC types, suggesting that in mice the MHC stimuli are used to avoid inbreeding. Mice can distinguish between paternally and maternally inherited genetic information carried by MHCs. In humans, women can detect and discriminate small variations in body scent related to MHC differences. In particular, a woman's sexual partner's scent choice is associated with inherited human leukocyte antigen (HLA) alleles. This choice is not related to the exposure to HLA-associated scents from her family during development. Moreover, the results from these studies show that there is no single most-preferred human male scent for everyone, but that scent preference is relative, based in this case on the degree of HLA differences between a man and a woman.

However, the social recognition in nature is vastly more complex, and involves the combined detection and integration of a variety of classes of chemosignals. Moreover, it appears reasonable that the same social cues can mediate different conspecific behaviors through the activation of each system.

The answer to the second question, as to how pheromones drive sexual behavior, relates to a repertoire of signals, among which those of particular interest are the chemosignals, which have been poorly investigated to date. In particular, odor, perfumes, and pheromones have been less investigated as related to male sexual behavior. Indeed, most of the information available concerns the female effects on this stimulation. Perfumes act in the first phase of sexual behavior, and they are involved with the hedonic perception of the mate. These cues can elicit greater judgment of human faces in terms of beauty and charm, over that of sexual interest and attraction, pleasantness and intensity, and liking and irritability, while having no influence on familiarity and confidence. Body odor associated with the follicular phase, as compared to the luteal phase, was judged significantly more pleasant and sexy. Indeed, men rate body odors associated with the ovulatory phase as more pleasant than odors associated with the non-fertile phase. Moreover, the female face and breasts show changes in morphology during the ovulatory phase, which are perceived as being more attractive to males. The female body temperature also changes during ovulation, and fascinatingly, exposure to the androstene 4,16-androstadien-3-one induces a heating

in a scattered pattern of the female face and body as a result of the neuroendocrine stimulation induced by 4,16-androstadien-3-one. Interestingly, these findings together raise serious doubts about the conventional scientific wisdom that human female ovulation should be concealed, and hence that men cannot detect when women are ovulating.

SCIENCE REVISITED 1

Odor is conscious perception that is induced by given odorants, which are small, volatile, and hydrophobic molecules.

SCIENCE REVISITED 2

Perfume is conscious perception provided by a combination of different odorants at defined concentrations. Perfume can elicit either pleasant or unpleasant perception.

The answer to the third question relates to the human spermatozoa that are released in the vagina, which swim actively along a complicated and tortuous path toward the egg for a blind date, or which follow a directed migration toward an attractant source. In species with internal fertilization, large numbers of spermatozoa are ejaculated directly into the female reproductive tract. These are sufficient in number for many to reach the egg, and so there is no apparent need for spermatozoon chemotaxis, although human spermatozoa are present within the fallopian tubes in numbers that represent only about 0.004% of the total motile spermatozoa ejaculated. Moreover, there is a significant difference between the spermatozoon distributions within the female tubes: the ovulatory tubal *ampulla*, where fertilization occurs, contains a significantly larger percentage of spermatozoa than the *ampulla* of the contralateral tube. As the chance of a successful chaotic collision between a spermatozoon and the egg within the tubal *ampulla* is statistically low, one of the mechanisms that may bring the two gametes together is indeed spermatozoon chemotaxis. Chemotaxis is directed movement toward or away from a specific chemical stimulus, and spermatozoon chemotaxis provides the modulation of the swim direction through a chemical gradient provided by an attractant. This phenomenon is also seen in the ancestral system of attraction between gametes of the opposite sex in marine sea urchins, coral, algae, and fish, which has remained in mammals through evolution.

Spermatozoon chemotaxis requires attractants in follicular fluid. In humans, several compounds have been hypothesized as responsible of this behavior, such as progesterone and atrial natriuretic peptide, among others. Since the discovery of the human odorant receptor, known as hOR17-4, this was debatable. The odorant receptors (ORs) constitute the largest multigenic family, which occurs on all of the human chromosomes except 20 and Y. The ligand specificity and functional importance of hOR17-4 has been demonstrated in transfected human embryonic kidney cells, and by the combination of bioassays and motion analysis of mature spermatozoon cells. Human spermatozoa respond to several classes of chemical stimuli. It has been chemically identified as the spermatozoon chemo-attractant known as bourgeonal, which act in a dose-dependent manner, from concentrations of 10^{-8} M. In this way, they navigate within this chemical gradient and show elevated swim speeds. Moreover, interestingly, the compound undecanal has been tested as a potential inhibitor of these bourgeonal effects on spermatozoon navigation and swim speeds. This all suggests that hOR17-4 signaling, at least, governs the chemical communication between spermatozoa and the egg. The amazing relationship found between the chemotactic activity of follicular fluid and the ability of the egg from

the same follicle to become fertilized strongly suggests that this spermatozoon chemotaxis through release of a pheromone has an important role in human sexual selection. In humans, only a small fraction of the spermatozoon population (≤10%) is chemotactically responsive, as compared to species that use external fertilization, where most of the spermatozoa are responsive, with this response changing with time: chemotactic spermatozoa lose their activity, whereas others acquire it.

Spermatozoa are selectively chemotactic only at the capacitated physiologic stage, where they can release the proteolytic enzymes that enable them to penetrate through an egg coat and hence fertilize an egg. Spermatozoa thus became chemotactically responsive during the capacitation process, and then lose this when that stage is concluded. Interestingly, the relationship between capacitation and chemotaxis is based on similar percentages (ranging from 2% to about 10%) and kinetics, and the continuous replacement of capacitated and chemotactic spermatozoa in a spermatozoon population. Deliberate depletion of capacitated spermatozoa results in the loss of this chemotaxis, and *vice versa*, and the capacitated state and chemotactic responsiveness of spermatozoa are synchronized and temporary, and they only appear once in the lifetime of a spermatozoon. This spermatozoon chemotaxis, which is directed by the pheromone released from an egg or from its surrounding *cumulus oophorus*, suggests that *in vivo* a selected population of spermatozoa will be recruited for the fertilization of an egg: the capacitated-chemotactic subset. Furthermore, continuous replacement of these capacitated-chemotactic spermatozoa ensures the availability of these spermatozoa for an extended period of time, despite the short lifespan of the capacitated state. Fascinatingly, a considerable fraction of the spermatozoa ejaculated into the female reproductive tract can be maintained with reduced motility in the oviductal isthmus. When ovulation occurs, some of these can resume their high motility and travel the distance from the storage to the fertilization site within minutes. This pheromone release by an egg, or by its surroundings, induces the chemotaxis that is required to increase the possibility for the egg to meet a capacitated spermatozoa as soon as ovulation occurs. This aspect is crucial in reproductive biology, and good functional chemotaxis, including pheromone release and odorant receptor expression, and capacitated-chemotactic spermatozoa could become a diagnostic tool for spermatozoon quality and male infertility. Moreover, this could be applied to the biological spermatozoon selection procedure before *in-vitro* fertilzation treatment, i.e. for intra-cytoplasmic single spermatozoon insertion or intrauterine insemination; the chemotactic activity of follicular fluid could be used to monitor the effects of different ovulation-induction protocols on the maturation status of oocytes aspirated for *in-vitro* fertilzation. On the other hand, this can also represent a new approach to contraception.

☆ TIPS & TRICKS 1

In humans, the capacitated physiological stage of spermatozoa, when they can release proteolytic enzymes that enable a spermatozoon to penetrate through the egg coat and fertilize the egg, is transient, with a life span of 50–240 minutes, and there is a continuous process of replacement of capacitated spermatozoa within a spermatozoon population.

Pheromone stimuli

The term pheromone originated from the Greek words *ferein*, which means to carry, and *hormon*, which means to excite. It was introduced by Karlson and Lüscher in 1959, when they identified bombykol, a female sexual pheromone of the silk moth (*Bombix*

mori) that is used to attract males over long distances. In 1961, Parkes and Bruce extended this concept of pheromones to mammals.

By definition, pheromones are essentially worthless chemical compounds that have been selected through evolution and they are combined in specific concentrations based on genetics, species, and individuals for release outside of the body. These can then be unconsciously perceived by another individual of the same species, which then start and/or modify and/or enhance and/or modulate specific physiology and behavior responses. Perceived pheromones induce programmed neuroendocrine changes and innate behavioral changes. The chemical natures of pheromones are wide, as they range from small volatile molecules of about 6 carbon atoms with a molecular mass of about 100 Da, to peptides or proteins, and steroids that can be combined as several compounds at different concentrations. Pheromones can be derived as or from catabolites of specific metabolic pathways. In the hamster, aphrodisin is a sexual pheromone that is synthesized in the liver and released in the urine, and is composed of a carrier protein and a volatile molecule. Curiously, the chemical structure of an elephant sexual pheromone is identical to the one of a moth; similarly, humans have a sexual pheromone that is the same as that of a boar.

☆ TIPS & TRICKS 2

Pheromones are not consciously perceived as perfumes or odorants. Pheromones act sub-consciously on the autonomic system, with regulation of the neuroendocrine system.

CAUTION 2

Human sexual pheromones are highly volatile in crystal.

In humans, it is still not known how many different pheromones are produced; however, some of these have been investigated, such as four putative sexual pheromones that are steroid derivatives. Three of these are secreted by the male, as 16-androstene derivatives from the metabolism of the characteristic male sexual hormones, the androgens and testosterone, which are secreted generally by the apocrine glands. These androstenes include: 4,16-androstadien-3-one (androstadienone), which is volatile and released in male sweat, saliva, and spermatozoa; the alcohol 5α-androst-16-en-3α-ol (androstenol), which is volatile, abundant in male sweat, and generally associated with a musk-like scent; and the ketone 5α-androst-16-en-one (androstenone), which is again volatile, discharged in male sweat, saliva, urine, and plasma (with the same concentration as testosterone), and generally associated with an unpleasant scent. It is important to note also that this scent arises only via the activities of micro-organisms. One pheromone that is secreted by females is derived from oestrogen, estra-1,3,5(10),16-tetraen-3-ol, and released in vaginal fluids. At the same time, both 5α-androst-16-en-3α-ol and 5α-androst-16-en-one are found in women, although at lower concentrations than in men. Other pheromones can be expected to be identified upon the examination of sexually dimorphic hormone metabolites, such as adrenal.

Pheromones can be classified chemically, behaviorally, and physiologically. The first classification is related to the chemical nature or structure of the molecule. The second is correlated to the behavior that can be induced, such as alarm, territoriality, identity, aggregation, imprinting, social organization and hierarchy, and adhesion and sexuality. The third is associated with the physiological processes that can control responses, of which there are 4 categories: releasers, primers, signalers, and modulators. Releaser pheromones generate instantaneous and reversible effects through the release of neurotransmitters in the central

nervous system (e.g. 5α-androst-16-en-3-one of the boar, which induces lordosis behavior in females on heat). Primer pheromones act on the endocrine and neurocrine glands, and they produce slower reactions, and are involved in reproductive and developmental physiology, for example modulation of puberty, the menstrual cycle, pregnancy, and in general, circulating hormones such as cortisol. This signaler pheromone carries gender, ownership, dominance, maturation level, and genetic information; for example MHC. Modulator pheromones modulate physiological processes: as enhancing or reducing.

Pheromone-releasing system

A pheromone-releasing system can be defined as an anatomical structure that can discharge chemical compounds that act on physiology and behavior. Pheromones exit the body in two ways: by lipid secretion, or by entrapment in a carrier protein, with the complex released in an aqueous medium. Pheromones can be synthesized in different anatomical structures or tissues of the releasing system. The main production regions in mammals are the preputial, perianal, sebaceous, apocrine, axillary, sub-jaw, Harder, brachial and lachrymal glands, and organs such as the liver, mouth, feet, and genitals. The body fluids that carry pheromones include urine, saliva, plasma, prostatic and vaginal secretions, tears and sweat.

☆ TIPS & TRICKS 3

The body fluids that carry human sexual pheromones are urine, saliva, tears, sweat, and prostatic and vagina secretions.

Androstadienone has been quantified in peripheral plasma in several studies in men, and it ranges from 0.01 μg/100 ml to 0.1 μg/100 ml unconjugated, and from 0.05 μg/100 ml to 0.1 μg/100 ml sulfate conjugated; in women androstadienone is about 0.036 μg/100 ml. Interestingly, the individual recognition-based lateralized cues that are secreted by the male brachial gland, which is a pair of specialized sebaceous glands, are molded by genomic determinants.

In humans, pheromone synthesis and release is the same as in other mammals, although there are some differences. Furthermore, the interactions between the secretions and the cutaneous microbial organisms complicate the pheromonal stimuli by adding a mix of odorants that are produced by the degradation of secreted substances, including pheromones. For instance, freshly produced apocrine secretion has no odor, being transformed into odorous products by micro-organisms. This chemical degradation can produce a mixture of volatile compounds that is consciously detected as the natural human body scent, or odor. However, characteristically, pheromones do not produce conscious perception in humans, besides a cognitive association process that can be noted normally when pheromones are sensed together with the perception of body scent. Male axillary sweat contains approximately 5-times more androstenone than female sweat, which is explained by sexually dimorphic levels of blood androgens. Also, there are sex differences in the colonization by micro-organisms, whereby the aerobic bacteria *Corynebacterium* ssp. transforms the odorless precursors androstadienol and androstadienone into the odorous 5α-androstenone in men, whereas in women, the dominant bacteria are *Micrococcaceae*.

There are apocrine glands associated with hairs in the genital area, around the navel, on the chest, breasts and areolae, and highly concentrated in the axillae. These glands develop in the embryo, but become functional only with the onset of puberty, which suggests a function closely connected to the levels of the steroid sex hormones, which increase with the onset of adrenarche and puberty. In addition to these glands,

humans have a high density of eccrine glands (watery sweat), which are involved in thermoregulatory processes, and sebaceous glands (sebum secreting). Interestingly, humans produce a greater amount of smelling secretions, as compared to other primates. The compounds released in sweat, saliva, and urine and which cover the skin and genitals, contribute to the hedonic quality characteristics of the natural human body scent. The vaginal barrel secretes "copulins," which are a mixture of C2-C5 aliphatic acids. These C2-C5 copulin concentrations vary through the menstrual cycle phases, as do their behavioral effects and odors. Thus, copulins are also referred to as pheromones.

SCIENCE REVISITED 3

Odor and perfume have only hedonic roles in chemosexual communication, with affects on charm and beauty judgements of exposed subject (Capparuccini *et al.* 2010).

However, the axillae are probably one of the most important sources of pheromones in humans, because the surface area for dispersal is also warmed to aid in volatilization, and they are positioned nearly at the level of the nose of the recipient when near another person. Several relaxing behaviors are also shown when children or mothers sleep near the axillae, such as the protective behavior with the male arm on the female shoulder, thus exposing the female to the male pheromones. Furthermore, the chemistry associated with the axillae can produce a mixture of compounds, among which there are C6-C11 normal, branched, and unsaturated acids that constitute the characteristic axillary odor. Interestingly, one of these acids, (E)-3-methyl-2-hexenoic acid (E-3M2H), is the most abundant, at around 357 ng/l in samples of secretions from the axillae of males, whereas the levels of androstenone are about 0.5 ng/l. In samples from females, the straight-chain acids are present in greater relative abundance than E-3M2H, which is at about 150 ng/l; though no androstenone can be detected. However, a related steroid, androstenol, was found here at 3.5 ng/l. Furthermore, the 3M2H Z-isomer has been identified in both genders, although in different relative abundances: 10(E-3M2H):1(3M2H Z-isomer) in males, and 16:1 in females. In addition, these acids are carried to the skin surface bound to lipocalin proteins, such as ASOB2, which is identical to apolipoprotein D (ApoD), has a molecular weight of 26 kDa, and has 3M2H as its bound ligand. Another recognized similar compound is 3-methyl-3-hydroxylhexanoic acid, which has a qualitatively cumin-like odor, which has been described as sweaty and pungent.

Another class of compounds released and involved in pheromonal communication is related to the MHC system. These are produced by the set of genes that code for immune function: the HLAs. HLAs have been detected in the lactiferous ducts of the breast, in sebaceous glands, and in axilla secretion. This strongly suggests that these secretions contain the unique signature of an individual that can be used for identification and can act as signaler pheromones. These compounds also have roles in mate choice, to avoid consanguinity.

Finally, the body-odor print consists of a bouquet of compounds, the relative amounts of which differ across individuals, and which include volatile consciously perceived molecules and the sub-consciously perceived pheromones.

TIPS & TRICKS 4

If the axillae are treated with strong antibacterial detergents, the production of androstenone decreases significantly.

Pheromone-sensing system

Pheromone-mediated sexual communication in humans has not been investigated comprehensively, generally because of its non-conscious, concealed nature, and the neglected functions of the vomeronasal or Jacobson organ. Indeed, it is commonly believed that pheromonal communication in mammals belongs to a unique and specialized pathway, the vomeronasal system, and that the main olfactory epithelium is exclusively responsible for sensing common odors. Conversely, a new perspective in pheromone perception has emerged following the discovery of a new class of evolutionarily preserved chemoreceptors, the trace-amine-associated receptors, which are involved in the detection of pheromonal cues.

In the traditional view, the main olfactory system and the accessory olfactory system form separate and parallel pathways, which are assumed to be involved in the detection of distinct sets of olfactory cues, odorants, and pheromones; this is known as the dual olfactory hypothesis. The perception of volatile chemical compounds, as odors, is carried out by the main olfactory system, which is considered to be a non-selective molecular analyzer, and which is responsible, in a large part, for the flavor of foods and beverages, as well as for numerous other chemically mediated aesthetic perceptions. For the pheromones, as volatile and non-volatile chemical compounds that trigger behavioral and endocrine responses, these are detected by the accessory olfactory system. In humans, the main olfactory system is located in the upper recesses of the nasal chambers, and is composed of the olfactory sensory epithelium (OSE) that lines the turbinates and part of the *septum nasi*. The turbinates are divided into: ethmoidal-turbinates, and their numbers vary according to species; the ectoturbinates, with 1 row in primates and 2 rows in many other mammals; and the endoturbinates.

The OSE is comprised of at least 6 morphologically and biochemically distinct cell types. The supporting, or sustentacular, cells are the non-neural component of the OSE, and they regulate the composition of the mucus, which protects the epithelium from damage from foreign agents and which contains xenobiotic-metabolising enzymes. The microvillar cells are located at the surface of the epithelium, and they extend axon-like processes to the olfactory bulb. The Bowman's glands and ducts, the 4th and 5th cell types, are formed of the globose basal cells and the horizontal basal cells. The globose cells act as multipotent stem cells for the renewal of the olfactory sensory neurons (OSNs), the 6th cell type. These OSNs are bipolar neurons, at the dendrite knob they have cilia that extend the ORs into the mucus flow. The axons of these cells together constitute the olfactory *fila*, which are formed by the ensheating glia. The OSN axons traverse the cribriform plate and *pia* matter, and make connections with the periglomerular cells in the olfactory bulb (Figure. 2.1). The olfactory bulb contains a remarkable number of neurotransmitters, while the OSNs release glutamate. The second-order neurons in the bulb are the mitral and tufted cells, which project directly into the primary olfactory cortex without synapsing in the thalamus. The olfactory cortex is composed of the anterior olfactory nucleus, the pre-piriform cortex, the lateral entorhinal cortex, and the amygdala. The cilia of the OSNs differ from the cilia of the cells of the respiratory epithelium, as they are much longer and lack dynein arms (and hence, intrinsic motility), and they express metabotropic receptors, the ORs, that are 7-transmembrane-domain G-protein-coupled receptors. There are approximately 1,000 OR genes in a human and a dog, and 1,500 in a mouse, although the percentages of pseudogenes also vary: 60%, 16%, and 20%, respectively. This is the largest known

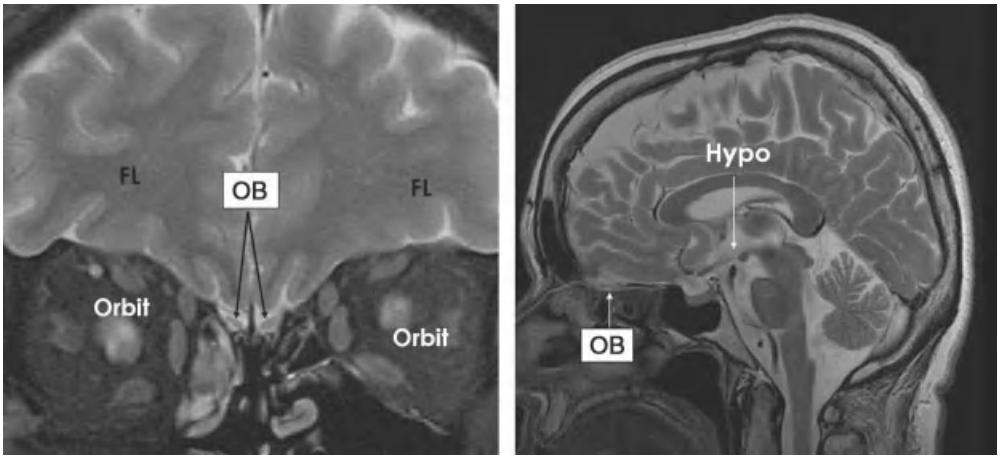


Figure 2.1. Coronal T2 Weighted image MRI shows olfactory bulb (OB); frontal lobe (FL), and orbits. Sagital T2 Weighted image MRI shows olfactory bulb (OB) and Hypotalamus (Hypo).

vertebrate gene family, and represents some 1–4% of all genes expressed. With the exception of chromosomes 20 and Y, all of the human chromosomes contain OR genes, which are mostly organized in clusters.

A unique type of OR is expressed in each OSN in mammals, which are derived from a single allele, and the neurons expressing a given OR type typically project their axons to 1, or at most 2, glomeruli within the main olfactory bulb. This implies that a given odorant activates a spatially defined or restricted set of glomeruli, and that at this early stage, the olfactory code is reflected not only as different patterns across the mucosa, but also across the glomeruli. Interestingly, OR expression is not tightly restricted to the sensory neurons in the nose. Ectopic OR transcripts have been found in a variety of tissues, i.e. myocardial and erythroid cells, ganglia of the autonomic nervous system (ANS), pyramidal neurons in the cerebral cortex, as well as the spleen, brainstem, colon, and prostate, and in spermatozoon cells. During the late stages of spermatogenesis, about 50 mammalian OR genes are found in the male germ-line cells. These ORs are localized to the mid-piece and base of the flagellum of the mature spermatozoon.

The vomeronasal organ is a cylindrical structure in humans, which opens into the nasal cavities between the *concha inferiori* and the *septum nasi*. It is organized into a sensorial epithelium that contains the vomeronasal sensorial neurons (VSNs), and supporting cells and basal cells. The VSNs are bipolar neurons with a microvillar structure at the knob, and they express the metabotropic vomeronasal receptors (VRs); in humans, it is not clear how many VR types are expressed (Figure 2.2).

These findings support the involvement in human chemo-sexual communication of a pathway that is mediated via the vomeronasal system and/or the main olfactory system. Despite these considerations, in humans, pheromones can elicit sexually dimorphic activation of the hypothalamus-amygdala areas, independent of whether they are sensed through the vomeronasal system or the main olfactory system, or both. This resembles a plesiomorphic plan of the mammalian pheromonal perception pathway, as has been shown in rodents, which show sexually dimorphic neuronal activation at multiple levels. Of particular interest, human pheromones activate the hypothalamus, which controls the ANS, a key structure

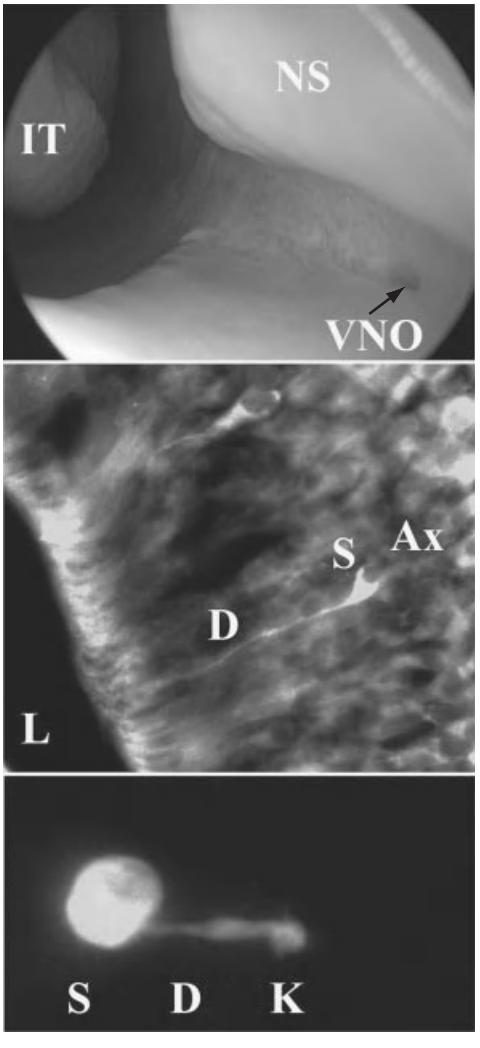


Figure 2.2. Endoscopic intraoperative view: Right nasal fossa. Vomeronasal organ (VNO) opening point out by the arrow is appreciable on anterior-inferior part of nasal septum (NS) opposite to inferior turbinate (IT). Vomeronasal sensory epithelium and isolated vomeronasal sensory neuron: axon (Ax); soma (S); dendrite (D); knob (K); and lumen (L).

in sexual arousal, sex-hormone release, and reproductive behavior, and thus autonomic parameters can vary in humans exposed to pheromones. In particular, androstadienone, a sex-steroid-derived compound, can induce dose-dependent and gender-specific non-conscious effects on ANS responses and on peripheral physiological activities and mood. A noticeable effect here is the variation in hedonic perception through the ovarian cycle that is associated with another putative human pheromone, androstenone, which elicits neutral or unpleasant smell sensations according to the ovulatory and non-ovulatory periods, respectively. Similarly, the preferences of women for male faces, voices, masculinity, and behavioral displays, and the neuromodulation of the reward system depend on the phases of the ovarian cycle. Although odorant perception and olfactory thresholds have been associated with the ovarian cycle and the hormone status, nothing has been specifically established with respect to pheromone perception and its relation to the ovarian cycle and hormone status. It has also been demonstrated that ovarian hormones can control sexual arousal and that women have a sexual arousal peak around ovulation.

However, we should not forget that the chemical perception systems are much more complex and might be involved in pheromone detection. The trigeminal system mediates the sensations of irritation, burning, cooling, and tickling, and can induce reflexive responses, such as secretion of mucus and cessation of inhalation, to prevent or minimize chemically or thermally induced injury to the nasal and pulmonary passages. The septal organ of Masera, which has now been identified in humans, is composed of a patch of sensory epithelium at the base of the septum, although its function is largely unknown. The terminal nerve, or *nervus terminalis* or cranial nerve zero, was discovered after the other cranial nerves had been named, and it is highly conserved, in terms of its remarkably constant anatomy across all of the vertebrate species, including humans. The terminal nerve is known for its high gonadotropin-releasing hormone (GnRH) content, and it ramifies throughout the nasal epithelium. Despite the

possibility that the terminal nerve has a sensory role in some species, i.e. the cetaceans, an endocrine role is supported by the demonstration that deficits in mating behavior occur in male hamsters after its central rootlets are severed, whereas tactile-induced lordosis in female hamsters is facilitated after such lesions. The GnRH content of the *nervus terminalis* is regulated, at least in part, by oestrogen.

SCIENCE REVISITED 4

The inability to sense a specific molecule is defined as anosmia, which can be genetically inherited or caused by permanent or temporary damage of peripheral receptors or neurons, for example during flu or following a trauma. Moreover, cognitive lack of ability to discriminate an odorant should be referred to cortical problems, such as Alzheimer disease.

Pheromone neurobiological-physiological effects

Androstadienone modulates the physiological mechanisms of emotional level, attention, mood, psychological state, arousal state, and the ANS in both sexes. It alters glucose utilization in brain areas: the subcortical and neocortex regions (prefrontal cortex, superior parietal area, and visual cortex). It has been found in both sexes at maturation, although at higher concentrations in males; indeed, females are more sensitive to lower concentrations of androstadienone, as compared to males. Moreover, the female peak in androstadienone sensitivity appears to be during the post-menstrual period. Notably, direct application of androstadienone to the vomeronasal sensorial epithelium induces a field potential that is also higher in females compared to males. Further studies have shown that androstadienone decreases breathing frequency and heart rate, and increases body temperature, cortical α-waves, parasympathetic tone, and gender-specific hypothalamic activation. Moreover, as well as these physiological modifications, when androstadienone is administered directly to the female VNO, it decreases embarrassment, anxiety, and stress. Interestingly, androstadienone can generate olfactory displeasure sensations, such as an intense urine smell or a musky odor, because of the molecule degradation from bacterial activity and/or light exposure, or at higher concentrations under artificial experimental conditions. Positron emission tomography investigations have shown clear activation of the hypothalamic and amigadala areas in the heterosexual female preoptic nucleus and ventromedial pars, while in the heterosexual male, only the olfactory areas are activated, which is also converse to the homosexual man, where the activation is in regions more like those of the heterosexual female.

CAUTION 3

Light and bacterial activity modify human sexual pheromones, by degrading them.

Androstenol is highly concentrated in male sweat, and female sensitivity to androstenol is higher than males and changes across the menstrual cycle. Moreover, androstenol alters luteinizing hormone (LH) pulsing when applied to the upper lip/nares region of female recipients.

Androstenone originates in the gonads and is secreted in human excretions at higher concentrations in males. It has been recognized in the rat as a sexual pheromone that is responsible for female lordosis during mating. In general, adult males are not able to perceive the odor of androstenone; however, a small fraction of the male population is particularly anosmic, while 40–50% have a slower

sensitivity to it. Sensitization can be induced with repetitive exposure to androstenone.

Extratetraenol shows physiological and psychological effects comparable to androstadienone; indeed, in heterosexual men, it activates hypothalamic and amygdala areas, and in particular the paraventricular and dorso-medial nuclei. In contrast, in heterosexual females, extratetraenol activates only olfactory areas, while in homosexual females it activates the hypothalamus, as in males.

For the HLAs, it is unclear which brain circuitry these activate, even if the physiological effects that they produce is inhibition of reproductive behavior, to avoid consanguinity.

The effects of pheromones on our emotions are linked to the consequences of their effects on the neuroendocrine system of the hypothalamic-pituitary-gonadal axis, which is itself a sub-conscious affect. In experiments on minimal conditioning to an arbitrary odor that was previously associated with a female, this will elicit a male LH response, even in the absence of the odor. The physiological significance of the conditioned change in LH secretion reveals the anticipatory appetitive sexual behavior and reinforces the idea that olfactory cues can activate the male pituitary-gonadal axis, mimicking the activation achieved by exposure to a female. Moreover, short-term exposure of heterosexual males to females induces increases in testosterone, through the link with LH. The female odor cues condition LH and testosterone release, and therefore the human hormone responses to non-olfactory sensory stimuli. Interestingly, this biological phenomenon does not require cognition because it belongs to the neuroendocrinology of behavior, and as a consequence, the sexual arousal of males can be classically Pavlovian conditioned. Pheromones probably induce GnRH-directed conditioning of human LH release, which evokes functional changes in the neuroendocrine pathways that mediate the release of testosterone and oestrogen, with or without any associated stimuli and without any involvement of cognition. LH might be a measurable link between sex and the human sense of smell. Moreover, it has been shown that cortisol saliva levels increase when women smell 4,16-androstadien-3-one. In addition, an aqueous mixture of 5 ovulatory fatty acids was shown to evoke increased saliva testosterone levels in men, and to produce improved judgments of female photos and of female voices than in controls. Thus, cognition and consciousness are exceeded by the effects of pheromones on the neuroendocrine system and on behavior. Several studies have shown the effects of androstadienone through brain imaging techniques, seen for the cortical processes, hypothalamus, and amygdala, and even when it is not detected consciously. Accordingly, human pheromones modulate the physiological and psychological state without being consciously discernible as odors.

CAUTION 4

Any odor or perfume, and even the scent of a rose, can become aversive when it is at too high a concentration. Thus, although pheromonal communication typically occurs without conscious knowledge, when they are produced in high concentrations and are degraded by microbial flora, pheromones can have both conscious and aversive effects on others.

Pheromonal pathology

Pheromonal regulation of male sexuality can be altered by genetic and inherited disorders, accidental and surgical VNO deafferentation, and behavioral disorders. The most important and longest studied genetic disorder

here is the X-linked Kallmann's syndrome. Patients are characteristically anosmic because of olfactory bulb atrophy, and consequently they have underdeveloped gonads and completely lack secondary sexual characteristics. This syndrome demonstrates an ontogenetic bond between pheromones and hormones and indeed results from underdevelopment of the olfactory bulb in the embryo. People with Kallmann's syndrome do not respond to human pheromones because of this neural structure atrophy. Furthermore, the human pheromones have effects on hormones such as GnRH, and thus on behavior. In normal subjects, GnRH neurosecretory cells of the hypothalamus derive from the olfactory placode, and then migrate into the hypothalamus. Conversely, in Kallmann's syndrome, this migration does not occur, which results in underdevelopment of the olfactory bulb and negligible secretion of hypothalamic GnRH.

Moreover, all genetic alterations or inherited diseases that involve the sensing organs, the limbic structure, or the hormone neurosecretory systems, with affects on specific protein functions (e.g. signal transducers, receptors, enzymes, neurotransmitters, ion channels, structural proteins, transporters, gene regulators), can affect pheromone sensing and perception. For instance, all animals display a repertoire of innate behaviors associated with mating and aggression. The exhibition of stereotyped mounting or aggression suggests that the nervous system is programmed to show these social and reproductive behaviors without a major requirement for learning or experience. This implies the existence of programmed neural circuits that govern innate behavioral repertoires, which are tightly regulated to assure that they occur in an appropriate social context. The developmental and temporal control of such behaviors can be mediated either by internal regulators, hormones, or by external cues, the pheromones. In mice, knocking out the TRP2 gene for cation channel, expressed predominantly in the VNO, provokes a dramatic reduction in the response to the pheromone. Male TRP2 mutants, in male-male interactions, fail to exhibit aggressive behaviors, while mounting is over expressed. As a consequence, mutant males assume a behavioral submissive role in respect to wild-type males. Surprisingly, male-female mating behavior is unaltered in male mutants, while mutant females show reduced female-specific behavior, including maternal aggression and lactating behavior. These results suggest that a genetic mutation could afflict sexual and social behavior in males. Furthermore, this indirectly implies the regulatory role of pheromone in eliciting innate behavioral responses.

Another incoming source for pheromonal alterations in the regulation of male sexuality is accidental or surgical deafferentation for functional and/or aesthetic reasons. In particular, the clinical demands for surgical correction include the reconstruction of biting and chewing functions, the correction of sleep apnoea syndrome, temporomandibular joint disorders, and cleft palate. Orthognathic surgery is often involved in correcting congenital or acquired jaw deformities. This is based on osteotomy that is achieved with the fracture line termed "Le Fort I," as it was originally described by Rene Le Fort. During bony structure reduction, a partial reduction of the inferior cartilaginous part of the nasal septum is also carried out, to prevent unfavorable and non-aesthetic nose bending; therefore, the VNO is often electrocoagulated to control the bleeding from the nasopalatine artery, or even completely removed. Indeed, in patients who have undergone septal surgery, they show a lack of the VNO, as compared to healthy individuals. In animal models, it has been demonstrated that the ablation or deafferentation of the VNO produces severe sexual

behavioral deficits in both males and females. Moreover, these experiments have demonstrated the role of memory in the process of recognition of pheromones through the VNO. Furthermore, as a result of VNO deafferentation carried out on more than 1,000 patients, there was a significant change in their sexual preferences and behavior, including their personal criteria for the choice of a mate. The arising hypothesis, which remains far from the standard ideas of pheromone effects, implies an inhibitory role of the VNO in terms of identification of inappropriate individuals for mating. This could be a plesiomorphic phylogenetically established function for the exclusion of inappropriate mates, in line with the good-genes and good-provider theories. Generally, it is assumed that pre- and post-delivery care of the mother is important for females. However, correct selection of a capable mother is important for males, and is crucial in humans because of the time needed for the pregnancy, and because the lactation period is longer than in other mammals. Thus, following this hypothesis, the inhibitory mechanism that is mediated via the VNO might be crucial in individual and gender recognition, and also to avoid consanguinity, while when the negative feedback is disrupted through surgery, the sexual behavior of the subject can be altered.

CAUTION 5

Changes in socio-sexual behavior in patients following orthognathic surgery have been observed. Depending on the clinical conditions, this surgery includes the reconstruction of biting and chewing functions, the correction of sleep apnoea syndrome, temporomandibular joint disorders, and cleft palate. This is based on osteotomy of the facial bones, and the need for the advancement or setting back of the upper and/or lower jaw bone, as performed for the fracture line called "Le Fort I." During this osteotomy, the VNO is excised together with the supplying nerve, in the course of the dissection of the nasal mucosa from the hard palate osseous base. As a result of this surgical intervention, the patient can lose the ability to recognize pheromones, which can significantly change their sexual preferences and behavior, including their personal criteria for the choice of a mate.

Behavioral disorders seen in males as higher aggressiveness and anxiety, sexual preference disorder, sexual inhibition, etc., might be generated by undeveloped or miss-developed pheromonal activity on the ANS, or by a shift in the reward system.

Pheromonal treatment

Diseases associated with altered hormonal states are usually treated with hormone therapies, although these can often have negative side effects. For example, Addison's disease is characterized by low levels of the hormone cortisol, and is treated with cortisol replacement therapy; this can cause peptic ulcers, osteoporosis, weight gain, mood disorders, and other pathologies. Human pheromones elicit changes in hormone levels; for example, a progesteronic pheromone alters LH pulsatility, such as the ovulatory-fatty-acid-evoked increase in saliva testosterone levels in men. These effects suggest a potential therapeutic mechanism, whereby merely smelling synthesized or purified human chemosignals might be used to modify the endocrine balance. In males, the LH/follicle-stimulating hormone (FSH) ratio controls testosterone production by the Leydig cells in the testes, which can result in stimulation of spermatogenesis. Sex steroid hormones alter neurotransmission by influencing synaptogenesis, synaptolysis, and apoptosis during development. GnRH

pulsatility is associated with changes in the release of LH and in FSH pulsatility, which have effects on the LH/FSH ratio, which, as indicated, modulates steroidogenesis. Thus, LH and the LH/FSH ratio are human measures of GnRH pulsatility. The effects of primer pheromones on GnRH thus mean that pheromones can influence LH/FSH ratios and the production of testosterone and oestrogen. More simply put, primer pheromones can influence the entire hypothalamic-pituitary-gonadal axis, which can influence behavior by alterations in the neuro-anatomy, and thus in the neurotransmission.

Moreover, 4,16-androstadien-3-one has an anxiolytic-like influence on positive mood. However, in contrast to typical anxiolytics, 4,16-androstadien-3-one increases rather than decreases sexual arousal. This dissociation highlights the potential advantage of triggering endogenous responses. Triggering endogenous mechanisms of hormone release can have several advantages over traditional hormone administration. Furthermore, we speculate that endogenous triggering of hormone release is likely to generate fewer negative side effects than exogenous hormone administration. Human chemosignals present a novel and more natural mechanism of endocrine therapy.

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3

Hormonal Regulation of Erectile Function, from Basic to Bedside (Androgen, Estrogen, Prolactin, GH, Thyroid Hormones)

Annamaria Morelli, Linda Vignozzi, and Mario Maggi

University of Florence, Florence, Italy

Introduction

Penile erection is a complex neurovascular event involving the interaction of psychological, neural, vascular, and endocrine factors, which are able to link the nervous system (and sexual stimuli) to the peripheral penile smooth muscle systems. Several neurotransmitters and endothelial factors have been shown to control erectile function by modulating the penile vasculature and smooth muscle tone of corpora cavernosa (CC), the two dorsal longitudinal structures constituting the erectile tissue of the penis. CC are essentially composed of large endothelium-lined vascular lacunae separated by fibrous trabeculae. In the flaccid penis, smooth muscle cells of CC are contracted and penile blood inflow is low. During erection, relaxation of trabecular smooth muscle results in an increased blood flow, pressure in the CC, and an expansion of sinusoidal spaces. The expanded CC cause mechanical compression of the emissary veins, which restricts the venous outflow from the cavernosal spaces and facilitate an entrapment of blood in the cavernosal sinusoids. This blood engorgement finally results in penile rigidity. The correct balance between relaxant and contractile factors is required to determine the functional state of the penis, finally resulting in a normal erectile function. Hence, the tone of penile smooth muscle is a key determinant of the hemodynamic events that maintain penile flaccidity or allow erection.

Peripheral relaxant mechanisms

At peripheral level, the most important and specific pathway for penile erection is the nonadrenergic/noncholinergic (NANC) parasympathetic nervous input, which through the release of a labile gas, nitric oxide (NO), leads to increased levels of cyclic guanosine monophosphate (cGMP) in penile smooth muscle cells. cGMP is one of the intracellular second messengers, which in turn triggers downstream signaling pathways culminating in CC smooth muscle relaxation. Formation of NO is strictly controlled by the activity of NO synthase (NOS) iso-enzymes, while cGMP degradation is controlled by phosphodiesterase (PDE) isoenzymes. Among the 11 members constituting the PDE family, PDE type 5 (PDE5) has been identified as the main enzyme responsible for the cGMP-hydrolizing activity

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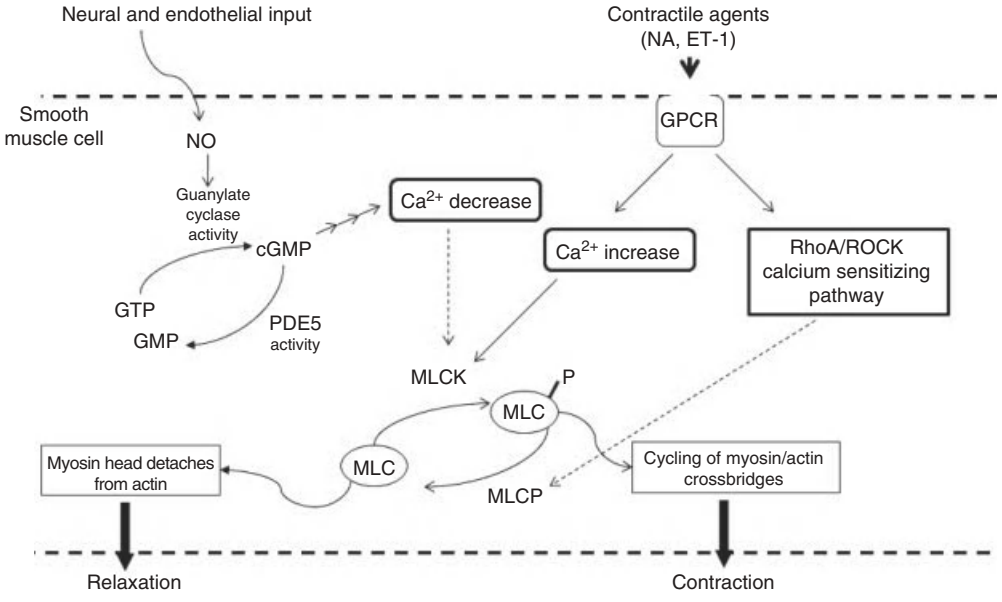


Figure 3.1. Intracellular signaling leading to smooth muscle cell contraction or relaxation in corpora cavernosa and determining the flaccid or erected state of the penis, respectively. NA, noradrenaline; ET-1, endothelin-1; GPCR, G-protein coupled receptor; NO, nitric oxide; GTP, guanosine triphosphate; GDP, guanosine diphosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase type 5; MLC, myosin light chain; MLCK, MLC kinase; MLCP, MLC phosphatase; Ca^{2+}, intracellular calcium concentration; black arrow indicates activation; dashed arrow indicates inhibition.

occurring in the penis. Hence, following sexual stimuli, NO release represents the initiation, while PDE5 activity represents the termination of erectile processes (Figure 1). Accordingly, PDE5 inhibitors (PDE5i), able to enhance the NO/cGMP-mediated signaling, represent the gold standard therapy for erectile dysfunction (ED).

Peripheral contractile mechanisms

Adequate intracellular levels of calcium and the sensitivity to calcium of the contractile machinery are required for the regulation of the penile smooth muscle tone. Smooth muscle cells contract when intracellular calcium concentration increases and relax when it falls. Therefore, besides the relaxant NO/cGMP signaling, other intracellular transduction signaling, mediating the opposite, contracted, status of the CC musculature, are crucial regulators of erectile function.

As shown in Figure 3.1, the binding of noradrenaline, endothelins, and prostanoids with their receptors on the surface of smooth muscle cells increases the intracellular activity of the membrane-bound enzyme phospholipase C, which through downstream mechanisms leads to a transient rise in the cytoplasmic free calcium concentration, finally inducing a calcium-dependent smooth muscle contraction. In detail, calcium ions at elevated levels bind to calmodulin, which changes its conformation and interacts with myosin light-chain kinase (MLCK). The resultant activation of MLCK determines phosphorylation of myosin light chains (MLC) and triggers the cycling of myosin cross-bridges along actin

filaments and the development of force. In addition, phosphorylation of the MLC also activates myosin ATPase, providing energy for the muscle contraction.

Although the increase of intracellular calcium is transitory, the smooth muscle cell is able to maintain the contracted status after the cytoplasmic calcium returns to the basal level. In fact, the so-called calcium-sensitizing pathways take over and consist of activation of receptors coupled to G-proteins that can also cause contraction by increasing calcium sensitivity without changing the intracellular calcium level. The most representative of such mechanisms involves the RhoA/Rho-kinase pathway, which is depicted in Figure 3.1. RhoA is a member of the small monomeric GTPase family, whose role is played not only in mediating smooth muscle contraction, but also in the regulation of several cellular processes, such as stress fiber formation and cell migration. When inactive, RhoA is localized within the cytoplasm. When contractile agents such as noradrenaline or endothelin-1 bind to their excitatory membrane receptors, RhoA is converted from an inactive to an active complex and translocates to the plasma membrane initiating signaling transduction. The best characterized downstream effector of RhoA is Rho-kinase (ROCK), which is directly involved in smooth muscle contraction. ROCK is a serine-threonine kinase that maintains MLC in the phosphorylated status with either direct or indirect phosphorylating activity, thus prolonging contractile tone, independently of intracellular calcium. RhoA and ROCK have been shown to be expressed in penile smooth muscle and, accordingly, a selective inhibitor of ROCK (Y27632) has been shown to cause relaxation of human CC *in vitro* and to induce penile erection in animal models. Moreover, pathological conditions associated to ED, such as hypertension, diabetes, and metabolic syndrome, exhibit over-activity of the penile RhoA/ROCK signaling, as demonstrated in experimental animal models.

Given their ability of allowing communication between cells in the same tissue as well as between different organs, hormones are essential for human physiology. In the male, hormonal regulation of physiology governing sexual function mainly refers to the role of testosterone, the male sex hormone. However, as reviewed in this chapter, hormones other than androgens, such as estrogens, prolactin, growth hormone, and thyroid hormones are involved in the regulation of male sexual response, including erectile function. Hormonal imbalances can account for 5% of the cases of men who suffer from ED. Moreover, different pathological conditions, which are characterized by comorbid ED, such as diabetes or metabolic syndrome, are also associated with hormone imbalance, mainly testosterone deficiency. Hormonal value assessment is therefore recommended in order to adequately treat ED patients.

Sex hormones and erectile function

Androgen

The role of androgens in the molecular mechanisms underlying erectile function has become clearer during the past decade. Besides the well-known role that androgens play at the central nervous system level as important modulators of male sexual behaviour including libido, recent advances about the relationship between androgens and erectile function at peripheral level have also been gained (Figure 3.2).

Trophic effect of testosterone on erectile tissue

A trophic effect of testosterone (T) on penile architecture has been demonstrated in different animal species. Androgen suppression via castration results in profound structural changes in penile tissue: apoptosis of the penile cavernosal and spongiosal cells, loss of elastic fibers in the tunica albuginea and, in the CC, loss of smooth muscle fibers, the essential penile component regulating

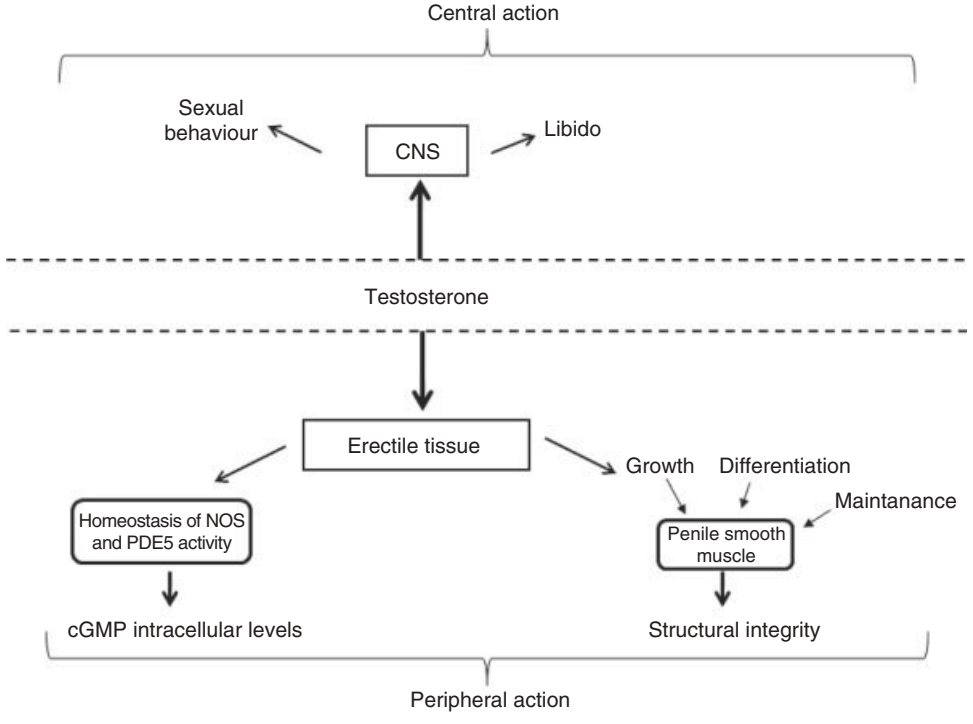


Figure 3.2. Testosterone targets in erectile function. Besides the central action on sexual behavior and libido, T also acts at peripheral level. By maintaining the correct balance between NOS and PDE5 expression/activity, T regulates intracellular cGMP levels in penile tissue and thereby smooth muscle relaxation for erectile function. On the other hand, T exerts a trophic and differentiating action for cavernous smooth muscle cells to maintain integrity of erectile apparatus.

detumescence and erection. Elastic and smooth muscle fibers are replaced by collagenous fibers, which may result in fibrosis. It has also been shown that T is involved in the maturation of penile tissue composition by promoting the commitment of pluripotent stem cells into the myogenic lineage and inhibiting their differentiation in adipogenic lineage. Androgen deficiency is associated with alterations in dorsal nerve structure and endothelial morphology, and accumulation of adipocytes in the subtunical region of the CC, which could impede blood outflow during sexual stimulation and contribute to venous leak. Thus androgens exert a direct effect on penile tissue, playing an important role in maintaining the integrity of erectile apparatus.

Effect of testosterone on relaxant/contractile mechanisms of erectile tissue

A number of different laboratory studies with experimental animal models have shown that T regulates both formation and degradation of the main relaxing factor cGMP in the penis, by acting on both NOS and PDE5 expression and activity. It has been demonstrated, in the rat, that androgen deprivation associated to several conditions, including aging and pathologies, such as type 1 and 2 diabetes mellitus (T1DM, T2DM), adrenalectomy, hypophysectomy, and castration, induced a

reduction of penile NOS expression with decreased erectile function that was reversed by androgen replacement therapy.

Recent laboratory findings in several species, including human, rabbit and rat, demonstrated that androgens are important for the regulation of cGMP degradation by modulating PDE5 expression and activity. Whether these laboratory findings could be extrapolated to human erections is still unclear. It has been speculated that the dual and antithetic role of androgens in promoting both the increase (initiation of the erection) and the decrease (termination of erection) of cGMP intracellular concentration in penile smooth muscle likely underlies an homeostatic mechanism through which the erections are finalized to sexual act and synchronized to sexual desire.

Beside the determinant involvement in penile NO-mediated relaxation and in erectile tissue integrity, T has recently shown a possible implication in regulating RhoA/ROCK-mediated penile smooth muscle contraction. Data from different animal models have evidenced that experimental T1DM was associated with the onset of an overt hypogonadism and with an up-regulation of RhoA/ROCK signaling in penile smooth muscle tissue. T supplementation in diabetic animals, by preventing the diabetes-associated hypogonadism, was able to normalize this calcium sensitizing pathway and, therefore, erectile response. How T supplementation prevented the amplified ROCK signaling is still unknown, but it is reasonable to believe that it might be secondary to the restoration of NO formation, even if a direct action of T on ROCK gene transcription cannot be ruled out. Deficient penile neuronal NOS (nNOS) expression is completely normalized by T administration to hypogonadal diabetic animals and NO signaling is supposed to down-regulate RhoA/ROCK pathway in the penis. Surgical castration in the rat was accompanied by hypersensitivity to the selective ROCK inhibitor Y-27632 and RhoA/ROCK over expression, which, however, was not fully restored by T administration. Therefore, further studies are needed in order to elucidate the precise molecular mechanisms through which T regulates the ROCK signaling pathway in penile and other smooth muscle tissues.

SCIENCE REVISITED

- Androgens exert a direct effect on penile tissue, controlling not only the formation of the main relaxing factor, cGMP by regulating NOS activity, but also the integrity of erectile apparatus.
- Recent laboratory findings demonstrated that androgens are also important for the regulation of cGMP degradation by modulating PDE5 expression and activity.
- The androgen-dependent PDE5 expression could explain the reduced effectiveness of PDE5 inhibitors in the treatment of ED in hypogonadal patients.

Although experimental findings have helped to better understand the mechanisms regulating human erectile function, a clear extrapolation to clinical aspects is still not reached.

Prevalence of hypogonadism in men suffering from ED has been assessed in several clinical studies. Serum T was below 3 ng/ml (10.4 nmol/l) in 12% of 7,000 men with ED compiled from 9 large series (including 4% of 944 men less than 50 years old and 14.7% of 4,342 men more than 50 years old). The real prevalence may be lower because most of those men had a single T measurement, sometimes in the afternoon, while circulating T decreases after 11 am in normal men, at least up to the age of 40. In one consecutive series of 1,022 men with ED, the prevalence of hypogonadism, based on 2 consecutive values <3 ng/ml before 11 am, was only 6.6%, including 4% before and 9% after

50 years old. The prevalence of marked hypogonadism (<2 ng/ml, 7 nmol/l) was even lower: 1.8%, including 0.8% before 50 and 2.6% after 50 years old. In another consecutive series of 2,794 men with ED aged 25–80 years, T measured only once, the most often between 7:00 am and 2:00 pm was <2 ng/ml in 7%, <3 ng/ml in 23%, <3.46 ng/ml in 33%, and <4 ng/ml in 47% of men. Measuring free T or bound T may unmask higher prevalence of low values (up to 37% and 24% respectively of ED patients aged more than 50 years).

Among men with ED, the most specific symptoms of associated hypogonadism are hypoactive sexual desire, decrease of nocturnal erections, and absence of any erection. However, clinical studies essentially evidenced a marginal effect of T on penile erections, thus suggesting that the decreased sexual activity in hypogonadal subjects is due to a decreased libido rather than to a direct effect of reduced T on the erectile process.

The effects observed in laboratory animals following a total suppression of T by castration may not be extrapolated without reservation to the consequences of the partial and often mild hypogonadism observed in most hypogonadal men with ED. All the more as men, unlike rats, produce dehydroepiandrosterone. Even in case of castration, this steroid may supply some T following peripheral conversion. Until now the data supporting the importance of T for the intrapenile mechanisms of erection are less substantial in humans. However, the expression of PDE5 is also T-dependent in our species, and some studies suggest T modulates the vascular mechanisms of erection in men too. Peak systolic velocity (PSV) of the cavernosal arteries, measured following intracavernosal injection of alprostadil in men with ED, severe T deficiency (T < 2 ng/ml), and no vascular co-morbidity, was significantly lower than the corresponding value of control men with psychogenic ED, and increased up to the range of the psychogenic group following 6 months of T therapy (173). Another study based on Color Duplex Ultrasound (CDU) of the cavernosal arteries, showed a highly significant correlation of the resistive index with the free T serum value. In a study of 20 arteriogenic ED patients with low normal T and non-responders to sildenafil, T therapy significantly enhanced the accelerating effect of sildenafil on PSV measured in the cavernosal arteries. Conversely, in a well designed, randomized, placebo-controlled trial, 24 men with severe organic T deficiency (mean age 35 + 12 years, T < 2 ng/ml, almost undetectable in most cases) and the same number of normal control men underwent nocturnal penile tumescence and rigidity monitoring for 3 consecutive nights, with administration of 50 mg sildenafil or placebo. The men with T deficiency were tested twice: at baseline and following T therapy for at least 6 months. In those men the single sildenafil administration restored normal sleep-related erections to the same extent of 6 months of T therapy, suggesting a relative independence of the peripheral mechanisms of human erections from T. Therefore, the few studies of the effects of T on the penile mechanisms of human erections have given inconsistent results.

More accordance has been reached between laboratory and clinical observations about the important role played by T in the responsiveness to PDE5i. In animal models, low levels of T severely hampered the PDE5i effectiveness, which was completely restored by T replacement. The explanation is that the drug efficacy depends on the availability of the target enzyme and, although the precise molecular mechanism has not been completely clarified, it has been shown that T positively regulates both expression and activity of PDE5, the main cGMP-catalysing enzyme in the penis. Several clinical studies suggest that hypogonadism is a risk factor for reduced response to sildenafil in men too. Accordingly, in ED patients with low T levels who do not respond to PDE5i, T replacement was able to rescue therapy. In men with ED and severe T deficiency, sildenafil failed to

increase the erectile response to visual sexual stimulation and this effect was restored following T therapy for 6 months. Lastly, sildenafil was able to restore the sleep-related erections with the same efficacy as T therapy and the effect of combining sildenafil with T therapy was greater than the sum of each of these two therapies alone as concerns every parameter of nocturnal erections.

T deficiency is often associated with pathological states, such as hypertension, T2DM mellitus and, as recently emerged, with metabolic syndrome (MetS), a clinical diagnostic category clustering several metabolic abnormalities (visceral obesity, dyslipidemia, hyperglycemia, and hypertension), which allows identification of individuals with high cardiovascular risk. Epidemiological studies showed that T2DM and MetS could predict the development of male hypogonadism, which in turn may be a risk factor for both metabolic (T2DM, MetS) and cardiovascular (CV) diseases. It has been recognized that subjects with MetS have a higher prevalence of sexual dysfunction, and in particular ED. In subjects with sexual dysfunction, the prevalence of MetS is an age-dependent phenomenon that, at mid-life, could affect almost half of the patient population. ED, the most commonly referred symptom of male hypogonadism, is regarded as a warning sign of MetS. Moreover, because of shared factors impairing both penile and systemic vascular blood flow, ED has been recognized as a sentinel sign of forthcoming CV diseases.

A recent study aimed at elucidating the pathogenetic relationships linking ED and hypogonadism with MetS has been performed in an animal model of high fat diet (HFD)-induced MetS in the rabbit. The results clearly demonstrated that MetS rabbits recapitulated the main clinical features of the human phenotype (hyperglycemia, dyslipidemia, hypertension, and increased visceral adipose mass). In addition, animals with HFD-induced MetS also showed an overt hypogonadotropic hypogonadism and penile abnormalities, including unresponsiveness to PDE5i, that closely resemble those observed in clinical studies. Interestingly, T supplementation to hypogonadal animals with MetS partially ameliorated not only penile alterations, but also the overall metabolic profile, normalizing visceral obesity, glucose tolerance, and blood pressure.

Concluding remarks

T is the main hormone involved in the complex dialog between the brain and peripheral organs controlling male sexual function. T deficiency affects the function of multiple organs and is frequently associated with age and co-morbidities. ED, the most commonly referred symptom of male hypogonadism, is often associated to pathological conditions affecting endothelial function and vascular system, such as hypertension, diabetes, and metabolic syndrome.

Normal T values are a prerequisite for erectile function in laboratory animals. Experimental data has shown that androgens exert a direct effect on penile tissue, regulating not only the integrity of erectile apparatus, but also the NO/cGMP/PDE5 intracellular signaling governing the functional status of penile smooth muscle cells. This T-dependent regulation of both cGMP increase (initiation of erection following NO release) and cGMP catabolism (termination of erection by PDE5 activity) confers to T the physiological action of timely adjusting the erectile process as a function of sexual desire, therefore finalizing erections to sex. In men, low T is often associated with reduced sexual desire and nocturnal penile erections, while association with sex-induced erection is less evident, thus suggesting that clinical aspects concerning T regulation of human erectile function are not fully clarified on the basis of laboratory studies. Of note, the androgen-dependent PDE5 expression seen in animal models fits well with the reduced effectiveness of PDE5i in the treatment of ED in hypogonadal patients. Together with this

aspect, the clinical evidence of hypogonadism co-morbid with aging and with pathologies associated with cardiometabolic risk factors, strongly support the importance to assess T plasma values in ED patients, not only for choosing the proper therapy but also for improving the overall quality of life.

☆ TIPS & TRICKS

The T-dependent regulation of both cGMP increase (initiation of erection following NO release) and cGMP catabolism (termination of erection by PDE5 activity) in CC underlies the main physiological action of T: to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections to sexual act.

Estrogen

The impact of estrogen on male sexual function strongly depends on its derivation from testosterone metabolism, via the enzyme aromatase. Testicular synthesis of estradiol is very low in males, where it is predominantly the product of peripheral aromatization of testicular and adrenal androgens. Concomitant with T reduction, estradiol values increase in aging and obese men. A decreased testosterone/estradiol ratio, which represents aromatase activity, correlates with conditions such as insulin resistance, hyperglycaemia or obesity, most likely because of reduced Leydig cell response to gonadotropins but, in addition, also due to the inhibitory action of estradiol on hypothalamic centers. Aromatase is mainly located in fat tissue and thus, obesity might trigger hypogonadism also by inhibition of gonadotropin release via the activated hypothalamic estrogen receptors. Estradiol has been shown to inhibit luteinizing hormone (LH) secretion in men (decreasing endogenous T synthesis) and to increase the liver synthesis of sex hormone binding globulin (SHBG; reduction of circulating available T).

High estradiol values are considered detrimental to male sexual function. The results from experimental studies indicated that a disruption in androgen milieu, with elevated estradiol levels and decreases in total T, may determine a direct, functional antagonism of T-related events of erection, likely mediated by estrogens. A reduction in smooth muscle and a relative increase in connective tissue in the CC after treatment with estrogens have been evidenced in animal studies. These results are in line with the loss of structural integrity in the CC of aging men and transsexuals undergoing estrogen therapy. Interestingly, estradiol values have been noted to be significantly higher in ED patients with venous leak than in controls, supporting the hypothesis that estradiol levels can adversely influence penile smooth muscle function. It has been demonstrated that estrogens may influence vascular reactivity in men and increase NO production by increased eNOS expression and activation, through both genomic and nongenomic mechanisms. Thus, estrogen could positively influence NO production and therefore erectile function, but this effect could be counterbalanced by lowering of free-testosterone levels. However, this estrogen effect on penile smooth muscle relaxation remains to be demonstrated, because direct incubation of rabbit CC strips with estradiol failed to induce a relaxant response. Actually, the androgen decline seems to be the major determinant for the impairment of NO-mediated erectile response and this effect is not influenced by the concomitant increase of estradiol levels. It is known that estrogens are not strictly required for a normal sexual function in men, as demonstrated in patients with congenital estrogen deficiency. Thus, estrogen action on erectile function could be primarily ascribed to indirect effects (negative feedback on hypothalamic-pituitary-gonadal axis and SHBG increase, thus lowering free T levels).

Alternatively, estrogen could influence other more recently investigated factors with a potential key role in erectile function.

A factor involved in ED may be vascular endothelial growth factor (VEGF), because of its known angiogenic effects and possible role as an androgen mediator. VEGF is a polypeptide secreted by a large number of cells that is mitogenic for endothelial cells and induces angiogenesis and vasculogenesis *in vivo*. It is also a potent stimulator of microvascular permeability and a chemotactic factor for endothelial cells and monocytes. VEGF has been shown to increase vascular permeability of post-capillary venules by inducing fenestration of the endothelium. These effects of VEGF could be mediated, at least partly, by the production of NO by endothelial cells. Treatment with intra-cavernous VEGF was able to reverse venogenic ED produced by castration in animal models. Moreover, different studies indicate that VEGF is under hormone controls since estradiol induces VEGF expression in human vascular smooth muscle cells and modulates VEGF effects in angiogenesis, vascular permeability, and integrity.

Venous insufficiency of the CC is the second most common cause of ED. A functional insufficiency of the venous system has been hypothesized, but the cause is not fully understood. It has been demonstrated that estradiol plasma concentration was significantly higher in ED patients with pure venous-leakage compared to control subjects and that estradiol level may influence venous vascular tone via VEGF or NO, thus affecting venous leakage dysfunction in these patients. These observations may explain a possible link between the high estradiol levels and a functional insufficiency of the venous system in ED.

Recently, a positive regulation of the RhoA/ROCK signaling operated by estradiol has been demonstrated in both rat and human bladder musculature, thus suggesting a procontractile role of estrogen on smooth muscle cells in the bladder. Whether this action could be exerted at level of other smooth muscle districts, such as CC, thus affecting erectile function, should be properly investigated in future studies.

☆ TIPS & TRICKS

- Detrimental estrogen action on erectile function could be primarily ascribed to indirect effects (negative feedback on hypothalamic-pituitary-gonadal axis, SHBG increase, increased peripheral aromatase activity), ultimately lowering physiologically available T levels.
- Observations also exist about a possible link between the high estradiol levels and a functional insufficiency of the venous system in ED.
- Hormonal imbalances leading to T deficiency is regarded the main cause of ED rather than the estradiol increase *per se*.
- Sex hormone determination is important in supporting potential therapeutic options in ED patients.

Prolactin and erectile function

Prolactin (PRL) is a 23 kDa-polypeptide secreted by pituitary lactotroph cells. Circulating forms of prolactin include, beside the usually predominant monomer form (23 kDa), high molecular forms such as macroprolactin (>100 kDa), a biologically inactive complex of PRL and IgG. PRL secretion is mainly inhibited by dopamine, via D2 receptors, and stimulated by serotonin and thyrotropin-releasing hormone (TRH), the three-aminoacid peptide, which stimulates also thyrotropin (TSH) secretion.

In mammals, the main physiological role of PRL during gestation is to prepare the breast for milk production, and during puerperium, to stimulate lactation. It is likely that PRL is also involved in the regulation of a variety of brain functions, overall directed to organize and co-ordinate behavioral and neuroendocrine adaptations during pregnancy and lactation.

In contrast to the importance of PRL in female reproduction, the physiological role of this hormone in males is still obscure. Gene

deletion of PRL or of its receptor does not alter male reproductive fitness, although this receptor is expressed in the brain, testis, male accessory glands, and even in the penis. Several studies have shown that PRL increases following male orgasm, hypothesizing a negative feedback control of this PRL surge on sexual motivation, contributing, therefore, to the post-orgasmic refractory period. However, it is noteworthy that the post-orgasmic rise in PRL is relatively modest and similar in men and women who are less prone to post-orgasmic refractoriness and satiety.

It has been demonstrated that a low PRL response to a serotoninergic challenge could be regarded a mirror of a blunted central serotoninergic function. Recent data indicates that also circulating prolactin, in the normal physiologic range, could mirror the central serotoninergic tone. In fact, among males consulting for sexual dysfunction, hypoprolactinemia (i.e. PRL levels in the lowest quartile) is associated with particular psychobiological features, often reflecting a low serotoninergic signaling. These include a higher prevalence of premature ejaculation (PE) and anxiety symptoms along with MetS and arteriogenic ED.

Although the physiological role of PRL in males is still poorly understood, the association between hyperprolactinemia (HPRL) and derangements in both the reproductive and sexual behaviors is better defined. The prevalence of mild HPRL (PRL >420 mU/L or 20 ng/ml) in male subjects with sexual dysfunction is variable (ranging from >13% to <2%). In these subjects, severe HPRL (SHPRL, PRL >735 mU/L or 35 ng/ml) is a relatively rare event (<1%). Milder forms of HPRL (MHPRL) do not play a significant role in the pathogenesis of male sexual dysfunction. Conversely, SHPRL has a negative impact on sexual function, impairing sexual desire – as well as erectile function – and T production. It has been demonstrated that in subjects with sexual dysfunction, a severely reduced libido is associated with a 10-fold increase in the prevalence of SHPRL. A PRL-induced hypogonadism, which is frequent but not constant, and results from a PRL-dependent decrease of LH secretion, could explain, at least partially, this association. PRL may also play a direct role in the control of male sexual desire. Among hypogonadal subjects with HPRL, prolactin-lowering drugs are able to restore both T levels and libido, while total T alone is not as effective.

The relationship between HPRL and erectile function is under debate. It has been well established that HPRL in man is associated with hypogonadism and ED. In these patients ED, as documented by the impairment of nocturnal penile erections, is likely to be due to organic rather than psychogenic causes, however, the exact site and mode of action of PRL is controversial. Some authors have suggested a possible pathogenetic link between severe ED and SHPRL. Among 51 patients with SHPRL and prolactinoma, an elevated percentage had a reduction of the nocturnal erections when compared to 51 age-matched normal controls (96.7% vs. 13.7%), although only 50% of the patients complained about sexual disturbances. The number of nocturnal erections correlated with the PRL levels. However, in a large series of 2,146 men with SD, a significant association between SHPRL and severe ED after adjustment for confounders has not been confirmed. A high portion (92%) of the studied population complained about ED and this may have reduced the chance of such an association.

In a mechanistic context, the hypothesized action of excess PRL at multiple levels within the hypothalamic-pituitary-gonadal axis to suppress serum T concentration does not explain why T replacement alone does not usually improve erectile function in hyperprolactinemic patients. Normalization of excess PRL appears to be essential for the reversal of ED, although there is a subset of patients in whom normalization of both PRL and T is required before ED could be corrected. Therefore, it has been speculated

that excess PRL may impair erectile function through mechanisms that are at least partially independent of T. In animal studies, it has been demonstrated that PRL directly and specifically produced contraction of the CC, resulting in erectile insufficiency, with an effect partially mediated by prostaglandin. However, additional data is required for clarifying the site(s) or mechanism(s) of such independent action of PRL on erectile processes.

SCIENCE REVISITED

- It is still unclear whether the negative effects of HPRL on erectile function are mediated centrally by affecting sexual interest, or through a direct effect of prolactin on CC smooth muscle contractility.
- A direct effect on the CC has been suggested in animal studies. In any case, the effect seems independent of circulating T levels and gonadal axis function.

Growth hormone and erectile function

Growth hormone (GH) is a 191-amino acid polypeptide synthesized and secreted, under control of growth-hormone releasing hormone (GHRH, positive) and somatostatin (SRIF, negative) of somatotroph cells in the anterior pituitary. Its secretion is also positively regulated by the 28-amino acid peptide ghrelin, synthesized primarily in peripheral tissues, such as stomach. The primary role of GH is to promote linear bone growth, through the promotion of insulin-like growth factor 1 (IGF-1) synthesis in the liver and other peripheral tissues. GH also has general metabolic effects that result in a positive protein balance. It increases lipolysis, which causes the release of free fatty acid from adipose tissue. Carbohydrate metabolism is also affected, through the stimulation of neoglycogenesis. The availability of this alternative fuel allows for the utilization of the spared proteins for growth. The GH receptor is a monomeric 620-amino acid protein of the class I cytokine-hematopoietin receptor superfamily, homologous with the receptors of PRL, interleukins 2–7, erytropoietin, and colony-stimulating factor. Each GH molecule binds to 2 receptors, forming a dimer that is directly translocated to the nucleus or primes a Janus kinase-2 (JAK2)-dependent cascade of intracellular phosphorylation, where signal-transducing activators of transcriptional proteins play a major role. This hormone is used clinically to treat children's growth disorders and adult GH deficiency. A number of factors are known to affect GH secretion, such as age, gender, diet, exercise, stress, and other hormones, as well as sex steroids. In particular, androgen stimulates, while estrogen inhibits, GH release. Both GH excess and GH deficiency may affect male sexual function, although the precise mechanisms are not fully elucidated.

The most common cause of GH excess is a syndrome referred to as acromegaly, due to a pituitary tumor composed of somatotroph cells of the anterior pituitary. Acromegaly is a relatively rare condition, with an estimated prevalence of 20–60 cases per million. Measurement of the serum concentration of GH or of its induced protein IGF-1 has become a pivotal criterion in both the diagnosis of the disease and the establishment of cure after appropriate (surgical and/or medical) treatment. The pituitary adenoma may become large enough to cause headaches, impair vision by pressure on the optic nerves, or cause deficiency of other pituitary hormones by displacement. Secondary hypogonadism is a relatively common feature of acromegaly. Accompanying problems can include muscle weakness, insulin resistance, and pressure on nerves, causing carpal tunnel syndrome. Cardiomyopathy and an increased mortality rate due to cardiovascular events are common. Although impotence

and decreased libido is often reported as a symptom of acromegaly, it is still unclear if it is due to the excess of GH or to the compression by the GH-producing tumor of the neighboring gonadotrophin producing cells. An excess of PRL, caused by mixed hyper-production of GH and PRL or by compression of the pituitary stalk, is a common feature of acromegaly, which can partially contribute to the sexual dysfunction. Moreover, due to the similarity of GH and PRL receptors, GH excess induces PRL-like effects and can induce galactorrhea. Patients with acromegaly have also prostate enlargement, which can be partially normalized upon disease control by surgery or medical therapy. It has been demonstrated that in acromegalic subjects, adequate surgical and/or medical therapy can also partially revert hypogonadism, although an irreversible hypogonadism has been described in those with larger adenomas. In none of these studies, acromegaly-related sexual dysfunction was investigated. In subjects with acquired GH deficiency in adulthood, GH supplementation increases prostate size, an effect that was further potentiated by androgen supplementation in those who were also hypogonadal. These findings suggest a direct relationship between GH/IGF-1 axis and prostate size, at least in the youngest subjects.

Less information is available about the effect of GH deficiency on male sexual function. Since in the aging male a progressive reduction of GH release and IGF-I synthesis has been described, the effect of GH, with and without T supplementation, has been tested in controlled trials. Only a small, short-term (1 month) controlled trial in older individuals that were not GH or T-deficient assessed sexual function. Neither GH nor T affected the number of sexual intercourses or mood. Concerning the possible effect of GH on the penile mechanisms of erection, it has been suggested that GH can induce peripheral vasodilation by increasing endothelial NO synthesis or activity through an IGF-1 induced effect or through a post-translational phosphorylation of eNOS. In addition, it has been demonstrated that GH supplementation enhances NOS-containing nerve fiber regeneration in both the intracavernosal and dorsal nerves after experimental unilateral cavernous nerve neurotomy in the rat. In isolated human penile strips, GH can induce a dose-dependent relaxation, along with an increase in cGMP. However, all these effects were obtained at a relatively high concentration of GH. A modest, but significant, increase in cavernosal concentrations of GH has been described during the physiological process of erection in men. However, such an increase is at least 3 orders of magnitude lower than those required to induce a 30% relaxation on *in vitro* human strips. In a study of ambulatory men, no correlation was found between peripheral GH levels and all the dimensions of the Aging Male Symptoms questionnaire, including sexual function. In a small series of patients with organic, but not psychogenic ED, peripheral GH levels were found to be lower than in age-matched controls. In the same study, the cavernous GH level, in both organic and psychogenic ED, was not different from the peripheral one.

☆ TIPS & TRICKS

- Prevalence of ED and reduced libido is increased in acromegalic patients. However, it is still a matter of debate whether GH has a direct role in inducing these disorders or if the cause of reported male sexual problems is the accompanying T deficiency or PRL increase.
- Due to the low prevalence of acromegaly in the general population, GH or IGF-1 determinations are not recommended as first line examination in male subjects with sexual dysfunction.
- Further studies on GH and erection are strongly encouraged.

Thyroid hormones and erectile function

The thyroid gland produces, under TSH control, two major active hormones, thyroxine (T4) and tri-iodothyronine (T3), which circulate in human blood tightly bound to carrier proteins. Free fractions of thyroid hormones are the biologically active hormones (FT4 and FT3), which regulate protein, fat, and carbohydrate metabolism. Hence, there are no organs or tissues even partially unaffected by thyroid diseases. For instance, both hypothyroidism and hyperthyroidism result in clear alterations in the cardiovascular and mental state. However, the association between thyroid diseases and sexual dysfunction in men has not been systematically studied until recently.

Clinical studies have evidenced an association between the hyperthyroid state and PE, which was substantially ameliorated by therapy of the thyroid disease. In a consecutive series of 755 men presenting with sexual dysfunction, a 2-fold greater prevalence of hyperthyroidism was evident among the men with PE. According to this finding, a small multicenter, prospective study, demonstrated that most (50%) hyperthyroid patients have PE, a prevalence that was substantially reduced (15%) by treating the underlying disease, with a consequent doubling of ejaculatory latency. However, no relationship between PE and thyroid dysfunction has been evidenced in a cohort of 620 men with life-long PE, thus suggesting that the association with hyperthyroidism is restricted to the acquired type of PE.

Medical treatment of the opposite state, hypothyroidism, resulted in a 2-fold decrease in ejaculatory latency and a reduction in delayed ejaculation. Hence, the view that thyroid hormones regulate the ejaculatory reflex is gaining credence. Clinical data also suggest that low sexual desire and ED may be related to hypothyroidism and can be normalized by thyroid hormones therapy. A role for hyperthyroidism-induced anxiety was also envisaged. A recent study in a limited number of ED patients indicated that ED is extremely common in males with thyroid dysfunction. Treatment of the latter restored erectile function.

SCIENCE REVISITED

- Thyroid function and erectile function frequently correlate.
- Hypothyroidism-induced PRL rise could mediate all the negative effects of thyroid hormones on male sexuality.
- A direct role of thyroid hormones on reproductive tissues, including the penis, has also been supported by the presence of thyroid receptors in rat and human CC. More studies are needed to clarify the role played by thyroid hormones in male sexual response.

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4

Testosterone and Other Hormonal Therapies (Antiestrogen, DHEA, Thyroid Hormones) for Erectile Dysfunction

Gianni Forti[1], Giovanni Corona[2], Linda Vignozzi[1], and Mario Maggi[1]

[1] University of Florence, Florence, Italy

[2] Azienda Usl Bologna Maggiore-Bellaria Hospital,Bologna, Italy

Erectile dysfunction was defined in 1993 by a NIH Consensus Development Panel as "the persistent inability to achieve and/or maintain a penile erection adequate for satisfactory sexual activity." According to the age of the male population sample and the different instruments (questionnaires, interviews) used by different authors, the reported prevalence of erectile dysfunction ranges from 50% in the Massachusetts Male Aging Study to 30% in a more recent European study performed on more than 3,000 European men aged 40–79 years (European Male Aging Study).

A normal erectile function is possible by the "normality" of 3 main components: the organic factor (good general health, neurologic and cardiovascular status, endocrine equilibrium), the intrapsychic factor (lack of stress, anxiety, depression), and the relational factor (a good couple relationship), which should all be explored when erectile dysfunction is present to establish the main cause(s) of this condition. The aim of the present chapter is to focus on the role of testosterone, DHEA, and thyroid hormones in the treatment of such prevalent condition.

Testosterone

Diagnosis of testosterone deficiency and treatment in men with erectile dysfunction and classic hypogonadism

Testosterone deficiency can be due to testicular failure (primary or hypergonadotropic hypogonadism) or to a pituitary or hypothalamic failure (secondary or hypogonadotropic hypogonadism). Testosterone deficiency in some subjects can be also caused by a combination of both primary and secondary hypogonadism, which is called mixed hypogonadism; however, this term is not generally used in clinical practice and is considered part of secondary hypogonadism. Several studies have also shown that a significant proportion of older men have testosterone

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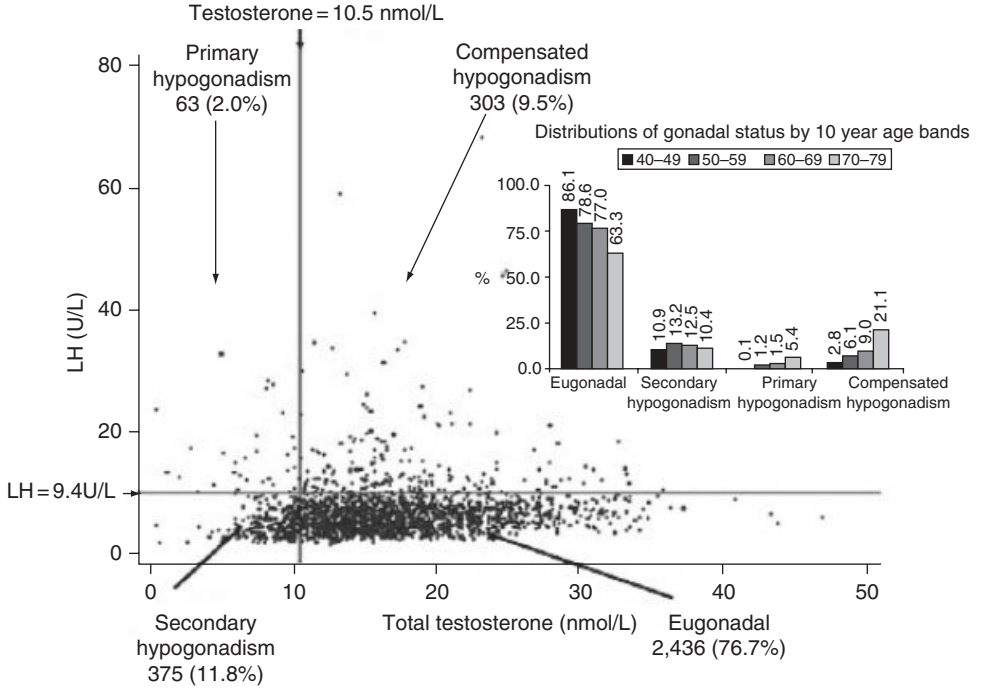


Figure 4.1. Using a threshold of 10.5 nmo/L for total testosterone (vertical line) and a threshold of 9.4 IU/L for LH (horizontal line), the majority of 3,177 subjects of the European Male Aging Study: (76.7%) were eugonadal; 11.8% had secondary hypogonadism; 2.0% had primary hypogonadism; and 9.5% had "compensated hypogonadism." The proportion of men with primary and compensated hypogonadism increased with age (inset), whereas the proportion of men with secondary hypogonadism did not increase (from Tajar *et al*. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *Journal of Clinical Endocrinology & Metabolism*. 95:1810–18. 2010, with permission).

levels in the normal range but high levels of luteinizing hormone suggesting the possibility of a state of compensated, or sub-clinical, hypogonadism that may eventually develop into overt primary hypogonadism, as it occurs for sub-clinical hypothyroidism (Figure 4.1). However, the clinical picture of male hypogonadism is mainly due to the time of onset, as congenital forms show a more severe phenotype than adult onset forms (Table 4.1).

In the *classic forms* with a definite etiology (Kallmann's syndrome, Klinefelter's syndrome, anorchia), erectile dysfunction is almost a constant symptom with a severity inversely related to testosterone levels: men with untreated congenital hypogonadotropic hypogonadism, without or with anosmia, have more severe erectile dysfunction because of testosterone levels in the female range and infantile genitalia, whereas in men with Klinefelter's syndrome, the presence and severity of erectile dysfunction is usually lower as testosterone levels are closer to the low-normal range for adult males (Figure 4.2). However, it has been reported that in Klinefelter men, erectile dysfunction is mainly due to low libido. As already reported in the Chapter 3, testosterone is an important modulator of the cGMP pathway

Table 4.1. Symptoms and signs of male hypogonadism according to age of onset

Affected organ/function	Before puberty	Adult onset
Libido and potency	Absent	Reduced
Voice	Infantile	Adult
Hair	Horizontal pubic hairline, diminished beard growth	Reduced body hair
Stature	Tall stature(eunuchoid)	Normal
Muscles	Underdeveloped	Reduced muscle mass
Prostate	Small	Reduced size
Penis	Infantile	No change of size
Testes	Small volume	Decrease of testicular volume

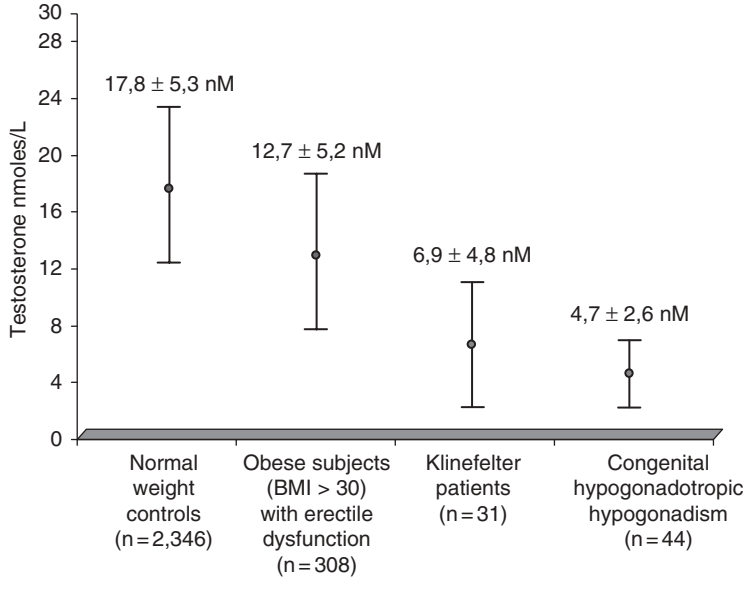


Figure 4.2. Mean levels of total testosterone in normal controls, obese subjects with erectile dysfunction, Klinefelter patients, and patients with congenital hypogonadotropic hypogonadism.

because it stimulates both cGMP and PDE5 synthesis. Accordingly, penile erections are possible even in severely hypogonadal men with testosterone levels comparable to those found in women, because the low production of cGMP is counterbalanced by the reduced PDE5 activity and therefore by a reduced cGMP hydrolysis. Penile erections can also be observed in children, and historical documents of daily life in ancient Rome report that eunuchs were able to have sexual intercourse with the women they served. Testosterone replacement in classic forms of hypogonadism is the cornerstone therapy, because it has beneficial effects not only on the libido and sexual arousal but also increases the volume of the ejaculate, the muscle mass and strength, beard and hair growth, bone mineral density, and prostate volume.

In adult-onset hypogonadism due to disorders of the hypothalamic-pituitary region, which are represented mainly by tumors, the main goal of treatment is the removal of the tumor (functioning or non-functioning pituitary adenomas, hypothalamic tumors), or its medical treatment such as in prolactinomas that can undergo a significant shrinkage with the dopaminergic drugs such bromoscriptine or cabergoline. However, testosterone treatment is indicated both before and after surgical removal of pituitary tumors to improve symptoms of testosterone deficiency including erectile dysfunction. Testosterone is also indicated in patients with large prolactinomas when dopaminergic treatment does not restore a normal secretion of gonadotropins and testosterone, because of the mechanical effects of the tumor on the pituitary gonadotropes.

However, classic hypogonadism is a relatively infrequent disorder with an incidence ranging from 1:500 (Klinefelter's syndrome) to 1:10,000–50,000 (congenital hypogonadotropic hypogonadism). An even lower incidence of 1:100,000 is estimated for pituitary adenomas.

☆ TIPS & TRICKS

Erectile dysfunction is a condition occurring in hypogonadal males. There are 2 main forms of male hypogonadism: the "classic" hypogonadism due to a definite etiology (Klinefelter's syndrome, congenital hypogonadotropic hypogonadism, anorchia, prolactinoma), which is not so frequent and with very low levels of testosterone (<7–8 nmol/L) and the so-called late-onset hypogonadism (LOH), which is much more prevalent, with milder signs and symptoms and testosterone levels often in a so-called "gray zone" (8–12 nmol/L), and with a multifactorial etiology mainly due to the effects of obesity and comorbidities.

Testosterone treatment in men with erectile dysfunction and adult or late onset hypogonadism (LOH)

In comparison to young hypogonadal males, the symptoms and signs of adult or elderly hypogonadal males are mild, insidious, and difficult to recognize. According to the recommendations of several international societies, the definition of LOH, also referred to as age-associated testosterone-deficiency syndrome, is "a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range)." The diagnosis of this condition is based mainly on sexual symptoms such as low libido, reduced morning erections, erectile dysfunction, and other symptoms such as decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. The presence of one or more of these symptoms must be corroborated with a low serum testosterone level. The measurement of serum testosterone performed with the widely used platform assays can give reliable results in the adult male range (10–35 nmol/L), but is much less accurate at concentrations lower than 10 nmol/L, so that mass spectrometry methods are now suggested, not only for research but also for clinical purposes.

CAUTION

The measurement of total testosterone with routine immunoassays is usually reliable in the normal adult male range (10–35 nmol/L), but is much less accurate in the hypogonadal range (i.e. for levels <10 nmol/L) as well as in women and boys. The clinician should ask patients to have testosterone measurements performed in a qualified laboratory. A low level of total testosterone in a man must be confirmed by a second measurement,

because it has been shown that in the second blood sample a normal level of testosterone will be found in about 30% of subjects.

Free testosterone levels can be useful when total testosterone is border-line or changes in SHBG are likely (obesity, aging). Free testosterone can easily be calculated using the calculator in the website of the ISSAM (International Society for the Study of the Aging Male): the values of total testosterone and of SHBG are needed.

There is now general agreement that in the near future testosterone levels should be measured with more accurate methods, such as mass spectrometry, not only for research but also for clinical purposes.

According to the above-mentioned recommendations, men with confirmed (2 measurements) total testosterone of less than 8 nmol/l (230 ng/dl), should be treated with testosterone, whereas men with total testosterone of more than 12nmol/(350 ng/dl), should not be treated. In the grey zone between 8 and 12 nmol/L, the measurement of free testosterone, which can be calculated by formulae using the concentrations of total testosterone and sex hormone binding globulin (SHBG), can be of help and a threshold of 225 pmol/L is suggested. The US Endocrine Society Guidelines suggests a more definite threshold of 10.4 nmol/L, but some members of the panel favored a lower threshold of 6.9 nmol/L. In the evaluation of a patient with low testosterone, it must be considered that low T can be due to a recent acute illness as well as to chronic conditions including obesity, metabolic syndrome, diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic disease, renal disease, HIV-related disease, and hemochromatosis. All these conditions should be excluded by a careful clinical evaluation and, if present, adequately treated.

In a recent large European study involving 3,369 randomized male subjects aged 40–79 years, from an initial pool of 32 candidate symptoms of testosterone deficiency, only 9 symptoms were confirmed to be related to the total or free testosterone levels with significant differences between the symptomatic and the asymptomatic men. These symptoms included 3 sexual symptoms (decreased frequency of morning erections, decrease frequency of sexual thoughts, and erectile dysfunction), 3 physical symptoms (reduced capacity of vigorous activities, inability to walk more than 1 km, inability to bend), and 3 psychological symptoms. The prevalence of the sexual symptoms was about 30%, whereas the prevalence of physical and psychological symptoms was lower than 10%. The study reported also that only the 3 sexual symptoms showed a syndromic association with low testosterone levels and that there was an inverse relationship between the number of sexual symptoms and a decreasing testosterone level. The conclusion of the study was that LOH can be defined by the presence of at least 3 sexual symptoms with a total testosterone level of less than 11 nmol/L (3.2 ng/ml) and a free testosterone level of less than 220 pmol/L. These thresholds are similar to that reported by the recommendations of the international societies mentioned above; however, due to the more strict criteria (presence of at least 3 sexual symptoms), the overall prevalence of LOH was 2.1%, much lower than in previous studies.

Recently, in a population of 2,000 men aged 20–79 years evaluated for sexual dysfunction and therefore symptomatic for hypogonadism, we found that using 8, 10.4, and 12 nmol/L as thresholds for testosterone, the percentage of hypogonadal males showed a progressive increase with age with a obvious higher prevalence with the higher 12 nmol/L threshold (Figure 4.3).

A significant inverse relationship between testosterone and severity of sexual symptoms was also recently confirmed in the same 2,000 subjects in whom both total and free testosterone showed progressively

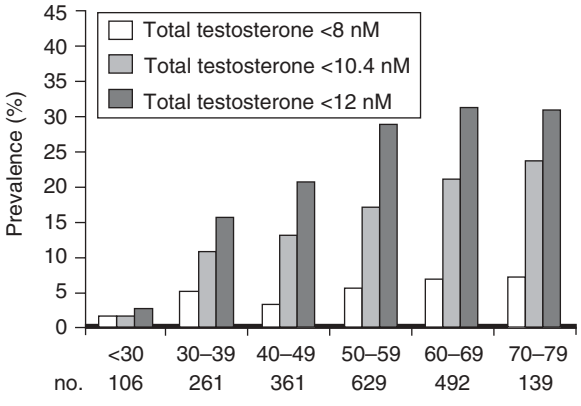


Figure 4.3. Prevalence of hypogonadism as function of different age groups and different cut-off levels of testosterone in a consecutive series of 1,988 male patients undergoing evaluation for erectile dysfunction (from Morelli *et al*. Which patients with sexual dysfunction are suitable for testosterone replacement therapy? *Journal of Endocrinology Investigation*. 30:880–8. 2007. with permission).

lower levels, in relation to the severity not only of hypoactive sexual desire but also of erectile dysfunction and of the decreased frequency of nocturnal erections: however, the progressively lower levels of testosterone were in the normal testosterone range for adult males. In contrast with these findings, no consistent correlation of total plasma testosterone with erectile function was found in 1,071 adult men aged 40–80 years, in whom the prevalence of erectile dysfunction of all degrees was estimated to be 53.9%.

The effect of testosterone administration in men with erectile dysfunction has recently been the object of a meta-analysis of 17 randomized-placebo controlled studies performed on a total of 656 middle-aged men of whom 284 were randomized to testosterone and 284 to placebo. The results of the meta-analysis have shown no consistent effect in men with erectile dysfunction and testosterone levels higher than 12 nmol/L. However, testosterone treatment was moderately effective on the number of nocturnal erections, sexual thoughts, and motivation in men with an average level at baseline below 12 nmol/L. The same study showed also that the effects of testosterone on erectile function were inversely related to the mean baseline testosterone concentration. A subsequent meta-analysis of the same papers evaluated the results of treatment according to the age of the men and reported a significant effect of testosterone treatment in the trials including young subjects, whereas no effects were found in the trials involving subjects aged more than 50 years.

Contraindications for testosterone replacement

Prostate and breast cancer are absolute contraindications for testosterone treatment. Relative contraindications are a serum PSA level of more than 4 ng/ml, a hematocrit of more than 50%, severe lower urinary tract symptoms caused by benign prostatic hypertrophy as defined by an International Prostate Symptom Score (IPSS) of more than 19, poorly controlled congestive heart failure, and untreated sleep apnoea.

Other beneficial effects of testosterone replacement

Testosterone treatment has significant effects on body composition, with an average significant increase in lean body mass of about 2.5 kg, and an average significant decrease in fat mass of about 2.0 kg, without a change of total body weight. Testosterone treatment in LOH men can also have a modest beneficial effect on

lumbar bone mineral density, which is inversely related to baseline testosterone levels, but no effect on femoral neck bone density. No data are available on the effects of treatment on bone fractures, either in patients with the classic forms of hypogonadism or in men with LOH. The effects of testosterone on muscle strength in older men are controversial, with some but not all studies reporting improvement in grip strength, and a few studies showing beneficial effects on lower limb muscle strength and significant effects on physical function and performance. An inverse relationship between testosterone levels and frailty – a combination of limitation of mobility and physical performance – has been reported, but the data on the effects of testosterone on frailty are very limited.

Some beneficial effects of testosterone treatment in type 2 diabetes mellitus and metabolic syndrome have been reported by some studies that were recently reviewed by 2 meta-analyses. However, due to the short duration of the trials and the limited number of enrolled subjects, testosterone treatment cannot yet be recommended for these conditions. Some small placebo-controlled studies have reported an improvement in cognition in men with LOH undergoing testosterone treatment, but this has not been confirmed by other authors.

☆ TIPS & TRICKS

Testosterone treatment in men with erectile dysfunction and "classic" hypogonadism has beneficial effects, not only on libido, sexual arousal, and erectile function, but also increases the volume of the ejaculate, the muscle mass and strength, beard and hair growth, bone mineral density, and prostate volume.

The efficacy of testosterone treatment in hypogonadal men is inversely related with testosterone concentrations.

Testosterone treatment for erectile dysfunction in adult men and LOH men is effective only when testosterone levels are below 12 nmol/L.

Potential adverse effects of treatment

The most important and frequent risk of testosterone treatment is the increase of the hematocrit above 50% (erhytrocytosis). The risk of erythrocytosis is higher in older men, as the stimulatory effect of testosterone on erythropoiesis is more pronounced than in young men. A recent meta-analysis of 19 studies, which included men over 45 years of age, showed that the risk of developing erythrocytosis in testosterone-treated men was 3.7-fold higher, compared to the risk of men treated with placebo. This finding was confirmed by a larger meta-analysis, which included men aged below 40 years of age. A potential increased risk of clinical prostate cancer is also a concern, as the prostate is an androgen-responsive organ. A recent meta-analysis has shown that the total number of prostate events (prostate biopsies, prostate cancers, serum PSA level >4 ng/ml, and increase in IPSS score) was significantly greater in testosterone-treated men than in placebo treated subjects (odds ratio 1.90 (95% Cl 1.11–3.24)). However, there was no difference in the rate of any event between the 2 groups. We must remember that it has been estimated that approximately 6,000 men aged 65–80 years with low testosterone levels should be randomized to placebo or testosterone treatment for 5 years to detect a 30% difference in prostate cancer incidence rates. No study of this size has yet been funded or is likely to be. Therefore, it is unlikely that we will know, in the next future, if long-term testosterone treatment can increase the risk of incidence of clinical prostate cancer.

According to recent recommendations, men with untreated congestive heart failure

Table 4.2. Testosterone preparations

	Formulation	Route of administration	Frequence of administration
Testosterone undecanoate	Capsules	Oral	120–160 mg/day (2–4 capsules)
Testosterone undecanoate	Oily depot	Intramuscular	1,000 mg every 12 weeks
Testosterone enanthate	Oily depot	Intramuscular	250 mg every 2–3 weeks
Testosterone Cypionate	Oily depot	Intramuscular	250 mg every 2–3 weeks
Testosterone	Hydroalcoholic gel 1%	Transdermal	50 mg/day
Testosterone	Hydroalcoholic gel 2%	Transdermal	40–60 mg/day
Testosterone	Patch	Transdermal	5 mg/day

should not be treated with testosterone. However, short-term studies have reported beneficial effects of testosterone administration in cardiac failure and a recent meta-analysis has shown that the rate of adverse cardiovascular events, such as atrial fibrillation, myocardial infarction, coronary artery bypass or graft, vascular events, and cerebrovascular accidents was not significantly different between the testosterone-treated and the placebo-treated men. Recently, testosterone treatment for 6 months of a selected population of elderly men (mean age 74 yrs) with low total testosterone (3–12 nmol/L) or free testosterone (<173 pmol/L), limitations in mobility and a high prevalence of hypertension, obesity, diabetes, pre-existing heart disease, and hyperlipemia, induced an increased rate of adverse cardiovascular events in comparison to the placebo-treated men. These findings suggest that caution is needed before starting testosterone replacement of aging men with poor health, low mobility, and multiple risk factors for cardiovascular events. Overall there is agreement that the short duration and the low number of subjects enrolled in most trials limit the conclusions that can be drawn regarding the cardiovascular risks of long-term testosterone replacement and further long-term randomized, placebo-controlled studies are needed.

Available testosterone preparations

Different testosterone preparations (oral, Ztransdermal, buccal, and intramuscular) are available, with variable pharmacokinetics and intervals of administration (Table 4.2). The clinician should discuss the cost, advantages, and disadvantages of different preparations with the patient, so that he can make an informed decision. In elderly males, short-acting preparations should be preferably used at the start of treatment, because rapid discontinuation of treatment is possible in the event of an adverse effect, such as an increase in hematocrit or serum PSA. The aim of the treatment should be to achieve total testosterone levels in a range that is mid-normal for healthy young men (14–17.5 nmol/L).

Duration and monitoring of treatment

According to recent recommendations, improvement of symptoms should be assessed after a few months of testosterone treatment. If no benefit is reported by the patient, treatment should be terminated and

other causes of symptoms should be investigated. If the treatment is effective, the patient should be regularly monitored by checking hematocrit and PSA levels, and by doing digital rectal examination every 3–6 months in the first year and then every 12 months thereafter. Testosterone therapy in men with classic forms of hypogonadism is usually life-long, as long-term safety, and follow-up studies of up to 10 years duration have been reported. On the other hand, the optimal duration of treatment for LOH men is currently uncertain, and controlled, long-term studies are needed to clarify this issue.

Summary

The presence of low libido, reduced morning erections, and erectile dysfunction requires the assessment of total testosterone. If morning (8–11 am) testosterone levels are lower than 8 nmol/L or between 8 and 12 nmoles and free testosterone is lower than 225 pmol/L in 2 measurements, after having excluded other possible causes of low testosterone (i.e. acute illness and chronic conditions including obesity, metabolic syndrome, diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic disease, renal disease, HIV-related disease. and hemochromatosis), testosterone replacement is indicated and the patient should be informed of the different characteristics, advantages, and disadvantages and costs of the different available preparations to make an informed decision. The patient should also be informed that the long-term beneficial and adverse effects of this treatment is known for young hypogonadal patients where long-term studies are available, whereas long-term randomized, placebo-controlled studies on testosterone replacement in elderly (>60 years) men with an often mild testosterone deficiency are lacking.

Antiestrogens (Clomiphene and Tamoxifen)

Clomiphene and Tamoxifen are very well-known molecules with antiestrogenic properties and are mainly used in women. Tamoxifen is largely used for treatment of breast cancer, whereas clomiphene is an ovulation inducer mainly used for treatment of anovulation in women with polycystic ovary syndrome. In males, Tamoxifen is currently empirically used for the treatment of idiopathic oligo-asthenoteratospermia, a frequent cause of male or couple infertility, characterized by a low sperm concentration, low sperm motility, and poor sperm morphology. Antiestrogens interfere with the normal negative feedback of sex steroids at the hypothalamic-pituitary level, where they induce a kind of deprivation status of sex steroids and therefore induce a compensatory endogenous secretion of gonadotropin-releasing-hormone and pituitary gonadotropins. In a male with a normally functioning hypothalamic-pituitary-testicular axis, the administration of Clomiphene or Tamoxifene is therefore followed by an increase of LH and FSH levels which, in turn, stimulate the Leydig cell steroidogenic activity/secretion and the Sertoli cell function, respectively. An increased testicular concentration of testosterone and a stimulation of Sertoli cells are supposed to stimulate and improve the quality of the spermatogenetic process. Even if Tamoxifen treatment is suggested as a possible option for treatment of idiopathic male infertility by the WHO manual for semen analysis, a recent Cochrane meta-analysis of 10 randomized studies involving 738 men has demonstrated that antiestrogens have a beneficial effect on endocrine outcomes of sub-fertile males, but do not significantly improve the pregnancy rate of the treated couples in comparison to controls.

The stimulatory effect of Clomiphene on gonadotropin and testosterone secretion has been the object of a relatively small number of studies mainly focused to restore testosterone secretion in male functional secondary hypogonadism, a condition frequently occurring (as already mentioned above) in acute as well as chronic illnesses.

Clomiphene was reported to revert hypogonadotropic hypogonadism in falciform anemia, uremia, alcohol and steroid abuse, and in sulpiride induced hyperprolactinaemia. Recovery of gonadal function by Clomiphene and improvement of erectile function was also reported in the majority of subjects of a group of males with prolactinomas under dopamine agonist treatment. A double-blind, placebo-controlled, crossover trial with Clomiphene citrate of 50 mg/day in 17 men with erectile dysfunction and secondary hypogonadism reported significant elevations of LH, FSH, and total and free testosterone, but no improvement of sexual function.

In a larger study performed in 178 men with secondary hypogonadism and erectile dysfunction, Clomiphene citrate administration for 4 months induced a significant increase of LH and free testosterone in all subjects, whereas full and partial improvement of sexual function was found in 39 and 36% of subjects, respectively, with no change in 25%. A multivariate analysis of the results showed that aging and the presence of chronic co-morbidities were important determinants of the small or absent effect of clomiphene on sexual function. In summary, Clomiphene is an antiestrogen that has been used mainly for research for treatment of secondary testosterone deficiency and, in some studies, also for the associated erectile dysfunction. Currently, Clomiphene is not indicated for either condition. Data on the effects of Tamoxifen in men with erectile dysfunction are apparently lacking.

DHEA

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are steroid hormones mainly secreted by the adrenal gland with a daily production rate of approximately 6–8 mg and 5–20 mg, respectively. The serum concentration of DHEA is in the nanomolar range (3–30 nmol/L), whereas DHEAS levels are much higher (3–12 μmol/L), because the metabolic clearance rate of DHEAS is very low. The physiological role of DHEAS is unknown, even if it is generally considered a large plasma reservoir of DHEA, since the 2 hormones can be interconverted by extra-adrenal sulphotransferase and sulphatase enzymatic activities. The lack of oscillations and the higher concentrations of DHEAS, as well the strict parallelism between the 2 hormone levels make the measurement of DHEAS easier and more reliable than the measurement of DHEA, so that DHEAS is the usually measured androgen to assess the adrenal secretion of androgens.

Both DHEA and DHEAS show an age-dependent pattern of secretion, with increasing serum levels at adrenarche and highest levels between 15 and 30 years of age. Then a gradual and progressive decline is observed and in the 8th–9th decade their concentrations are only 10–20% of those observed in young adults. As no specific receptors are known for DHEA, both DHEA and DHEAS are considered as hormone precursors exerting indirect androgenic and estrogenic effects following peripheral conversion into small amounts of testosterone and estradiol. The importance of the conversion of DHEA in testosterone is likely to be more important in women than in men, in whom the adrenal and testicular contribution to the pool of circulating testosterone, the main androgen, can be estimated as 5 and 95%, respectively.

The age-related decrease of DHEA and DHEAS is much more marked than the decrease of testosterone and has also been linked to the phenotypic changes of aging such as increased fat mass and reduced lean mass, visceral adiposity, reduced bone mineral density and increased risk of fractures, decreased quality of life, cognitive impairment, and increased risk of cardiovascular events. DHEA and DHEAS secretion is stimulated by ACTH; however, there are many discrepancies between adrenal androgen

and glucocorticoid secretion, leading to the general opinion that an additional "cortical androgen stimulating hormone (CASH)" is responsible for the control of the secretion of adrenal androgens. Many putative CASHs have been proposed, including POMC derivatives, prolactin, and IGF-1, but conclusive proof is lacking. Evidence for a separate adrenal androgen-stimulating hormone is provided by:

1) the fall of DHEA with aging and illnesses, whereas cortisol secretion is unchanged; and
2) the unchanged secretion of cortisol at the time of adrenarche.

In recent years, several randomized placebo-controlled studies lasting 6 months to 2 years have assessed the efficacy of DHEA administration to elderly adults. Most of these studies were performed in post-menopausal women and the results, in contrast with cross-sectional studies indicating a link between low DHEA levels and impaired sexual function, well-being, and cognitive performance in post-menopausal women, did not show significant benefits of oral DHEA administration for any of these outcomes or favorable effects on lipids and carbohydrate metabolism.

An inverse relationship between DHEAS levels and the incidence of erectile dysfunction has been reported by large studies, such as the Massachusetts Male Aging Study. These data are partly confirmed by a smaller study reporting a DHEAS level significantly lower in 309 healthy men with erectile dysfunction with respect to 133 age matched controls, but only under the age of 60. According to these findings, some trials have evaluated the effect of DHEA supplementation in men with erectile dysfunction. In a prospective double blind, randomized, placebo-controlled study, 20 subjects with erectile dysfunction and normal levels of testosterone, prolactin, PSA, and a serum DHEAS level below 1.5 μm/L were treated for 6 months with an oral daily dose of 50 mg of DHEA and 20 control subjects with placebo. DHEA treatment was associated with higher mean scores for all 5 domains of the International Index of Erectile Function (IIEF), with no modification of serum levels of testosterone, Prolactin, and PSA; however, the real statistical significance of the differences between the 2 groups was unclear. The same authors in another subsequent study treated 4 different groups of patients with erectile dysfunction of different etiologies with oral DHEA 50 mg/day for 6 months and found a significant increase in the scores of questions 3 and 4 of the IIEF (ability to obtain vaginal penetration and to maintain erections) in the patients with no or mild organic etiology but not in patients with diabetes or neurologic disorders. In a more recent study, 79 men with sexual dysfunction and low levels of testosterone or DHEA received oral testosterone undecanoate (80 mg twice daily; n = 29), DHEA (50 mg twice daily; n = 28), or placebo (n = 29) for 6 months. The effects on sexual performance were evaluated using 4 different questionnaires (IIEF, Androgen Deficiency in the Aging Male, Aging Male Symptom Scale, Global Assessment Questionnaire). No significant improvement of sexual interest or erectile function was observed between the 3 groups, suggesting no clinical benefit of DHEA or testosterone supplementation in men with low testosterone or low DHEAS.

Overall, in agreement with the weak biological action of DHEA, an androgen exerting its biological effects by its minimal conversion to testosterone, there is no rational for treating erectile dysfunction with DHEA, even in men with low levels of adrenal androgens and/or testosterone.

Thyroid hormones

The relationship between erectile dysfunction and disorders of thyroid function was reported as a common finding, but was anecdotal up to a few years ago when some

studies reported the prevalence of erectile dysfunction and other sexual symptoms both in hyperthyroid and hypothyroid men. Some authors administered the Sexual Health Inventory for Males (SHIM) to 27 hyperthyroid and 44 hypothyroid men before and 1 year after initiation of treatment for thyroid dysfunction and found a SHIM score of 21 or less in 78.9% with thyroid dysfunction and in 33.8% of controls. A positive correlation was found between SHIM scores and serum-free thyroxine levels ($r = 0.413$, $p = 0.005$) and negative for TSH ($r = –0.669$, $p < 0.0001$). One year after treatment, the SHIM score was significantly increased, both in hyperthyroid and hypothyroid patients. Another small study has evaluated the prevalence of sexual symptoms in 34 subjects with hyperthyroidism and 14 with hypothyroidism. The prevalence of hypoactive sexual desire, premature ejaculation, and erectile dysfunction was 17.6, 50.0, and 14.7%, respectively in hyperthyroid men, whereas 64.3% hypothyroid men complained of hypoactive sexual desire, delayed ejaculation, and erectile dysfunction. Medical treatment of both conditions induced an improvement of erectile dysfunction, as well as of the other sub-domains of sexual function in several patients, but due to the small number of recruited subjects no statistical significance was reported. TSH and thyroid hormone levels also normalized after treatment, with changes in serum sex steroids reflecting the changes in SHBG levels. Overall it is obvious that the use of thyroid hormones is indicated only in hypothyroid patients and that the beneficial effects on erectile dysfunction (when present) are mainly due to the cure of the main condition.

CAUTION

The administration of antiestrogens such as Clomiphene and Tamoxifen in adult men stimulates the secretion of gonadotropins and testosterone. The effects of Clomiphene in the treatment of erectile dysfunction have been evaluated in selected subjects for research purposes, but currently has no rational in clinical practice.

DHEA is an adrenal androgen with a very low androgenic activity due to its conversion to testosterone. Beneficial effects of DHEA administration have been reported mainly in ovariectomized or post-menopausal women, whereas the evidence of its efficacy in men with erectile dysfunction is poor. Therefore, DHEA should not be used for the treatment of erectile dysfunction.

Disorders of several aspects of sexual function (low libido, premature or delayed ejaculation, erectile dysfunction) have been reported both in hyperthyroid and hypothyroid subjects. A beneficial effect of treatment of both conditions on different domains of sexual function has been reported by a few studies. *L-Thyroxine* should be used for treatment of erectile dysfunction only in symptomatic hypothyroid men.

Conclusion

In conclusion:

1) the treatment of erectile dysfunction with testosterone should be used only in hypogonadal men;
2) the measurement of testosterone and the normal ranges should be obtained by a qualified laboratory;
3) no beneficial effect can be expected by testosterone treatment of men with erectile dysfunction and testosterone levels higher than 12 nmol/L;
4) LOH men should be informed that the long-term benefits and risks of testosterone treatment are not yet known and that further randomized, placebo-controlled studies are needed;

5) the treatment of erectile dysfunction with antiestrogens, DHEA, and thyroid hormones in clinical practice is not supported by evidence-based data.

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5

Risk and Benefit of Androgen Deprivation Therapy in Prostate Cancer

Giovanni Corona[1], Mauro Gacci[1], Elisabetta Baldi[2], Gianni Forti[2], and Mario Maggi[2]

[1] Azienda Usl Bologna Maggiore-Bellaria Hospital, Bologna, Italy

[2] University of Florence, Florence, Italy

Introduction

Prostate cancer (PC) is the leading type of cancer in men in the United States, with 186,000 new cases in 2008 and 28,600 deaths. It is the second major cause of death due to cancer in US men after lung cancer. Similarly, in Europe, PC is the most common solid neoplasm in men, with an estimated mortality rate for 2011 varying from 12.6 and 8.1/100,000, with the highest rate in Poland and the United Kingdom, and the lowest in Italy. Declines in PC mortality are expected both in Europe and in the US. A decline was already observed in France, Germany, and the UK between 1994 and 2004, but trends were still upward in Poland and approximately constant in Italy and Spain. This is likely attributable to improvements in disease diagnosis and, chiefly, treatment. In addition, although PC is one of the most prevalent types of cancer in men, many subjects never have symptoms, undergo no therapy, and eventually die of other causes. This is because PC is, in most cases (~2/3 of cases), slow-growing, symptom-free, and, since men with the condition are older, they often die of causes unrelated to it. Only 30% of cases are aggressive and develop quickly. Current treatment options for clinically localized or locally advanced cancer of the prostate include radical prostatectomy, radiation therapy, brachytherapy, cryotherapy, or "watchful waiting." Depending on a man's age, slow-growing cancer can often be left alone and monitored, while aggressive cancers demand urgent action. Androgen deprivation therapy (ADT) is the cornerstone in the treatment of advanced and metastatic PC. The following sections will specifically analyze the relationship between androgens and the pathogenesis of PC as well as the role of ADT in the treatment of PC, emphasizing advantages and possible related adverse events.

Androgen regulation of prostate growth

Huggins and Hodges, almost 70 years ago, gave rise to the clinical concept of the androgen dependence of PC, with the

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demonstration that castration caused regression of the PC. Later, Wilson first hypothesized that the main androgen inducing prostate growth was not testosterone (T), but its highly biologically active metabolite dihydro-T (DHT), which is formed locally from T by the action of 2 5α-reducing isoenzymes, 5α-reductase type 1 and 2, the latter being predominant. Accordingly, large randomized, placebo-controlled clinical trials have shown that using type 2 selective (finasteride) or unselective (dutasteride) inhibitors of 5α-reductase reduce the risk of PC. Despite this evidence, the role of androgens in the pathogenesis of PC is still controversial. Several population-based studies failed to show a significant association between circulating levels of androgens and increased risk of PC. Conversely, low T levels have been found to be associated with advanced, high-grade PC. It has been suggested that low androgen levels can increase selection for phenotypes resistant to hormonal therapy, which may also be more aggressive. Whether low T levels are the cause or the consequence of the observed higher PC risk is a matter of speculation. Low T could be a marker of a pre-existing and/or more aggressive PC and not an independent risk factor for PC.

CAUTION

Androgens are vital for growth and maintenance of prostate; however, low, rather than high, serum T levels are more likely associated with advanced PC.

The "saturation" hypothesis

According to the Morgentaler hypothesis, the human prostate is sensitive to massive androgen ablation (castration levels), but rather insensitive in normal or even in subnormal conditions (such as in mild hypogonadism) since in physiological situations the androgen receptor (AR) is "saturated" by the circulating androgens and therefore rather insensitive to further T increase. This hypothesis has been substantiated by both experimental and clinical evidence. Binding of androgen to AR shows a saturation curve with a steep increase in binding seen with increasing androgen concentration up to a plateau, representing maximal binding due to the filling of all binding sites. Further increase in androgen concentration does not result in any further binding to AR. An example of this concept is reported in Figure 5.1, showing results from our laboratory on the effect of increasing concentrations of T on human prostate stromal cells, obtained from patients with benign prostatic hyperplasia (BPH). As a function of time, untreated BPH cells progressively increase in number, especially when exposed to T. However, concentrations higher than 1 nmol/L did not further increase BPH cell proliferation, suggesting a saturation model (Figure 5.1, inset). In other words, it can be speculated that T at sub-physiological concentrations promotes prostate growth, while when in the physiological male range (10–30 nmol/L) it does not further stimulate proliferation.

Similar data were derived from animal studies. Examining the effects of varying doses of T on prostate re-growth in the castrated 55-day-old Sprague-Dawley rat, it has been reported that total prostate wet weight, DNA content, and secretory activity all increased with increasing serum T concentration reaching a plateau at higher T doses. The half-maximal response was observed at serum T concentrations in the mean-castrate range of ≤36 ng/dl corresponding to a human concentration of approximately 50 ng/dl (1.7 nmol/l).

We recently confirmed this evidence in 2 different large clinical series of subjects consulting for erectile dysfunction (ED). In particular, we found that prostatic specific antigen (PSA) levels were androgen-dependent only in hypogonadal men, whereas this correlation disappears with

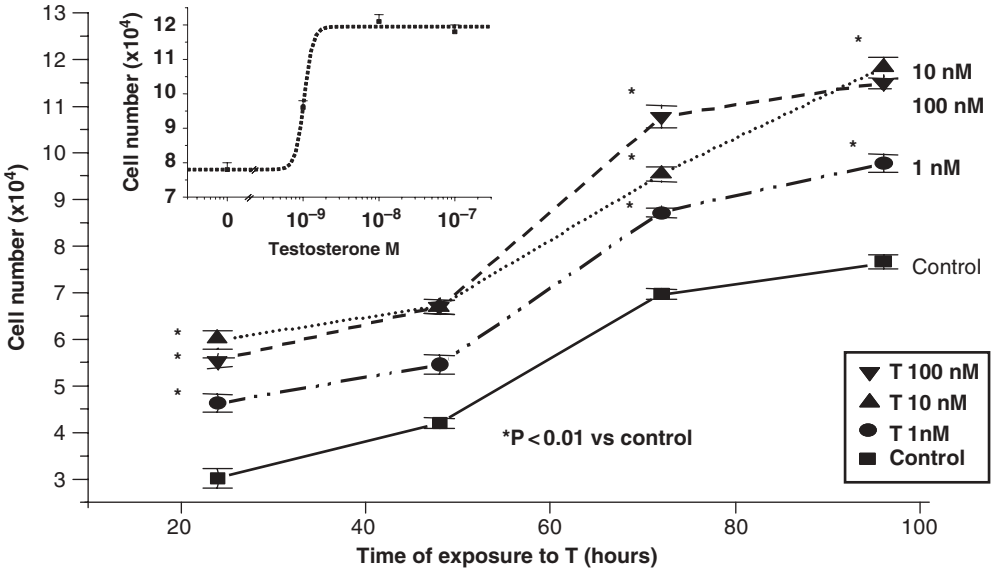


Figure 5.1. Effect of androgens on benign prostate hyperplasia (BPH) cell growth. Time course (24–96 h) of BPH cell proliferation in the absence (control) or presence of different doses of T (1 nM; 10 nM; 100 nM). Results are the mean ± SEM of three separate experiments performed in quadruplicate. Inset: Effect of 48-h incubation with increasing concentrations (10^{-9}–10^{-7}M) of T on BPH cell proliferation. Results are expressed as the percent increase (mean ± SEM) over their relative controls in three different experiments performed in triplicate. Adapted from Corona G, Baldi E, Maggi M. Androgen regulation of prostate cancer: where are we now? *Journal of Endocrinol Investigation*. 2011.

higher levels of androgenization (Figure 5.2, Panel A). In particular, when the association between PSA and T was evaluated as a function of T deciles, the upper 9 groups had similar PSA values, while the lowest (below 8.2 nmol/L, which roughly corresponds to 231 ng/dL) demonstrated a significantly reduced PSA at ANOVA (p = 0.005). A further increase of T levels was not associated with a significant rise in PSA. Figure 5.2 (Panel B) also shows the PSA-T association in a selected sample of subjects apparently free from prostatic diseases, as a scatter plot of PSA vs. T, along with the best-fitting regression line. In line with what was observed as a function of T quartiles, the PSA regression graph is almost linear at low T values and plateaus at T levels of about 8–10 nmol/L. Similar results were observed in patients with PC undergoing radical prostatectomy or after ADT. Hence, the "saturation point" approximately corresponds to the clinical threshold for the diagnosis of hypogonadism. In conclusion, according to the "saturation" model, prostate cells are already maximally stimulated at the physiological T concentration. At physiological T concentration, no evidence suggests a link between androgen levels and PC risk, although there is no controversy over the fact that lowering the T serum to castrate levels at least temporarily induces PC regression. However, over time, PC inevitably becomes resistant to ADT and survives in an androgen-independent (AI) state.

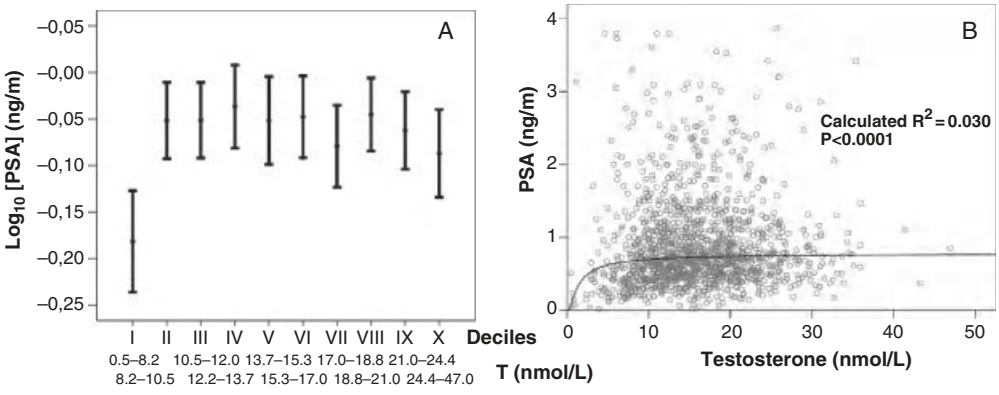


Figure 5.2. Panel A: PSA levels as a function of total testosterone deciles in a consecutive series of 2,757 patients attending our Unit seeking medical care for sexual dysfunction. ANOVA Tukey *post hoc* was $p < 0.005$ for 1st decile vs. 2nd or higher. Panel B: Relationship between testosterone and PSA levels as a scatter plot along with a best-fitting regression curve. Data derived from a selected sample of 1,377 patients attending our Unit seeking medical care for sexual dysfunction and apparently free from prostate diseases: history of prostatitis, BPH, or suspected prostate cancer as assessed by urological examination and/or an abnormal (tender, enlarged, or with suspect nodules) digital rectal examination of the prostate, and/or total PSA above 4 ng/ml, and/or previous prostatic surgery or radiotherapy, and/or using drugs altering prostate growth (testosterone, alpha-blockers, vitamin D, and antiandrogen drugs including GnRH analogues, bicalutamide, 5-alpha-reductase inhibitors, serenoa repens, and mepartricin.) Adapted from Corona G, Baldi E, Maggi M. Androgen regulation of prostate cancer: where are we now? *Journal of Endocrinology Investigation*. 2011.

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- Experimental, animal, and clinical evidence has demonstrated that prostate cells are already maximally stimulated at the physiological T concentration, the "saturation model".
- According to this hypothesis, T regulates prostate growth only in hypogonadal conditions.

Molecular mechanisms of androgen-independence

The molecular mechanisms leading to the development of AI prostate cancer (AI-PC) have not yet been fully understood. Essentially molecular events that drive transition to AI can be essentially divided into those involving the AR and those that bypass it.

Mechanisms involving AR

Several lines of evidence suggest that amplification and mutations of AR may be involved in the AI process. Studies in human tumor specimens demonstrated that amplifications of AR are found in about 30% of AI-PC tumors and appear to develop as a consequence of ADT, as they are not present in the original tumors. Conversely, AR mutations that confer ligand promiscuity may be present also in hormone naïve PC, but appear to be more frequent and more aggressive in AI ones. Other mechanisms include alterations of AR co-regulatory molecules, found to be increased in AI tumors, ligand-independent

activation of AR, and increased intra-prostatic androgen levels.

AR bypassing mechanisms

The activation of alternative growth pathways such as PI3K/AKT/mTOR, has been considered as another possible mechanism in the development of AI. In these situations, apoptotic pathways are inhibited and proliferation continues in a low/suppressed androgen environment. Activation of the PI3K/AKT/mTOR pathway may also lead to activation of AR, further supporting AI growth of the cells. In addition, a recent study has demonstrated that, in therapy resistant cells, only a minority of genes are androgen regulated: most of AR-dependent genes are indeed down-regulated, conferring enrichment in cell functions related to invasion and migration as well as growth.

Another relevant event occurring during the development of AI is neuroendocrine differentiation (NED). The incidence of NED in prostate tumors is considered a promising prognostic indicator for the development of AI disease. In fact, neuroendocrine cells, do not express AR, and produce and secrete serotonin and other peptides able to profoundly influence the surroundingenvironment.

The role of AR in prostate cell differentiation/prostate cancerogenesis

Animal and experimental models have demonstrated a differential role of AR in PC, depending on its location (differentiating in the epithelium, oncogenic in the stroma). Similarly, *in vitro* studies have shown that enforced expression of AR in AR-negative PC cells may decrease the metastatic/invasive potential of the cells. There are also clinical data supporting a differentiating role of AR in PC and demonstrating promotion of metastatic lesions following ADT. Indirect support comes from the clinical evidence that intermittent ADT benefits patients with regards to PC progression.

Intraprostatic androgen synthesis

Intraprostatic androgen synthesis may contribute to increased proliferation, as well as transition to AI and progression of PC. Indeed, intra-prostatic androgen levels may remain elevated in PC patients undergoing ADT. Accordingly, it has been reported that the expression of the enzymes AKR1C3 and SRD5A1, that convert, respectively, androstenedione to T and the latter to DHT, are abundantly expressed in PC, implying that blocking intra-prostatic T conversion may represent a favorable therapeutic option for AI-CP.

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Molecular mechanisms leading to the development of androgen-independent prostate cancer includes:

Mechanisms involving androgen receptor:

- Androgen receptor amplification
- Mutation of androgen receptor
- Amplification/deregulation of androgen receptor coactivators
- Local androgen production

Mechanisms bypassing androgen receptor:

- Alternative growth pathways
- Growth factors
- NED

Advantages of ADT in patients with PC

As previously discussed, ADT is the cornerstone in the treatment of advanced and metastatic PC. The use of ADT has significantly increased over the last few years from 3.7% in 1991 to 31% in 1999. In particular, it has been reported that about 30% of men diagnosed with PC in the US have received ADT (600,000 men). However, it is important to clarify that there is clear evidence that ADT

improves disease-free and overall survival only under 2 conditions: 1) in combination with primary radiation for locally advanced or high-risk diseases; and 2) as an adjuvant therapy for positive lymph node (pN+) diseases after prostatectomy. Since the 5-year relative survival for men with all stages of PC combined is more than 98%, it is reasonable to think that a "misuse and/or abuse" of ADT has occurred in the past few years. The following sections will specifically analyze these points.

CAUTION

- ADT improves disease-free and overall survival only under 2 conditions;
- In combination with primary radiation for locally advanced or high-risk diseases;
- As an adjuvant therapy for positive lymph node (pN+) diseases after prostatectomy.

Adjuvant vs. neo-adjuvant ADT

In a Cochrane meta-analysis comparing neo-adjuvant and adjuvant ADT for localized and locally advanced PC, neo-adjuvant therapy prior to radical prostatectomy did not improve survival (Hazard ratio, HR: 1.11; 95% confidence interval, CI: 0.67 to 1.85, p=0.69), even if there was a significant reduction in the positive surgical margin (HR 0.34, 95% CI 0.27 to 0.42, p<0.00001) and a minimal reduction of disease recurrence rates (HR 0.74, 95% CI 0.55 to 1.0, p = 0.05), in favor of treatment. Neo-adjuvant therapy prior to radiotherapy significantly improved overall survival for Gleason below 6, and allowed a significant improvement in disease-free survival (HR 1.86, 95% CI 1.93 to 2.40, p<0.00001). In addition, after adjuvant ADT following prostatectomy, a significant improvement in disease-free survival at 5 years (HR 3.73, 95% CI 2.30 to 6.03, p<0.00001) and 10 years (HR 2.06, 95% CI 1.34 to 3.15, p=0.0009) has been reported. Conversely, adjuvant ADT following prostatectomy did not significantly improve overall survival at 5 years (HR 1.50, 95% CI 0.79 to 2.85, p=0.2). However, at the same time, adjuvant therapy after radiotherapy had a significant overall survival gain apparent at 5 years (HR 1.46, 95% CI 1.17 to 1.83, p = 0.0009) and 10 years (HR 1.44, 95% CI 1.13 to 1.84, p = 0.003).

Combined ADT vs. monotherapy

In a systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma, no statistically significant difference in 2-year survival between men treated with combined ADT and those treated with monotherapy (20 trials: HR = 0.970; 95% CI: 0.866–1.087) has been reported. Conversely, a 5-year survival rate seems better after combined androgen blockade compared with monotherapy (10 trials; HR = 0.871; 95% CI, 0.805–0.942), even if significant treatment related adverse events leading to withdrawal from therapy occurred more often with combined androgen blockade.

The Prostate Cancer Trialists' Collaborative Group (PCTCG) published an individual patient data meta-analysis of combined ADT, showing that non-steroid antiandrogens conferred a small but statistically significant reduction in all causes of death over castrate therapy alone (72.4% v 75.3%; HR, 0.92; p = 0.005). In a double-blind, placebo-controlled trial on bicalutamide vs. flutamide, in addition to a luteinizing-hormone-releasing hormone (LHRH) agonist, a decrease in all-cause mortality has been observed for patients randomly assigned to bicalutamide, which did not reach statistical significance (HR, 0.87; 95% CI, 0.72 to 1.05; p = 0.15). Combining these results (bicalutamide vs. flutamide and flutamide vs. castration), PCTCG reported a calculated HR of 0.80 (95% CI, 0.66 to 0.98) for bicalutamide combined therapy vs. castrate therapy alone.

Early ADT vs. Deferred Therapy

One of the most critical issues is to determine when to start ADT while patients are asymptomatic, given the known toxicities of this treatment. In a systematic review including 4 trials involving 2,167 patients, the overall survival at 1, 2, 5, and 10 years for the early treatment group was 88, 73, 44, and 18%, while for the delayed therapy it was 86, 71, 37, and 12%, with an estimate of PC specific survival favored by early therapy (the risk differences at 2, 5, and 10 years were 2.7, 5.8, and 4.6%, respectively).

In the first outcomes from the European Organization for Research and Treatment of Cancer (EORCT) trial on early vs. delayed endocrine treatment for N+ PC patients, with a median follow-up of 9.6 years, the HR for survival on delayed vs. immediate treatment was 1.23 (CI 0.88 to 1.71), indicating a 23% insignificant trend in favor of early therapy.

In the last update on this topic, a 22% increase in the HR of death of those subjects randomized to delayed treatment has been reported (HR = 1.22, 95% CI 0.92, 1.62). The difference was not statistically significant and median overall survival on immediate ADT was 7.6 years (95% CI, 6.3–8.3 years) vs. 6.1 years (95% CI, 5.7–7.3 years) in the delayed ADT group.

Intermittent androgen blockade

In a recent study comparing the efficacy of intermittent (IADT) vs. continuous ADT (CDAT) for patients with hormone-naive advanced or biochemical recurrent PC, the estimated 3-year AI disease rate was significantly lower in the IADT group (7.0 ± 4.8%) than in the CADT group (38.9 ± 11.2%; log-rank p = 0.0052).

In a recent review including data from 19 phase 2 studies, IADT generally showed comparable efficacy to CADT with respect to various oncological outcomes, such as biochemical recurrence and overall survival. In particular, IADT was significantly better than CADT with respect to 3-year risk of progression in 1 study, and it demonstrated tolerability benefits, particularly with respect to sexual function.

Androgen supplementation to hypogonadal PC

Since the "saturation model" emphasizes the concept that PC growth is not androgen-dependent in non-castrated men, the possibility of offering testosterone replacement therapy (TRT) to symptomatically hypogonadal PC subjects whose cancer has been successfully treated has been addressed by several case report studies. So far, results of TRT after radical prostatectomy have been reported in 6 studies (206 patients), while 2 studies have evaluated TRT after radiotherapy (11 patients) and 1 after brachytherapy (31 patients). In addition, a recent study has evaluated the effect of TRT in 13 symptomatic testosterone-deficient men with untreated cancer (Gleason score 6 in 12 subjects and 7 in 1 patient) with a median follow-up of 2.5 years. The vast majority of patients were not associated with PC progression or clinical recurrence. Only 1 study, collecting records of 96 patients who received TRT after initial management for PC from 2000 to 2007, showed that nearly 60% of men had increasing PSA levels that triggered discontinuation of TRT, even though biochemical progression was not associated with clinical or symptomatic disease progression. However, in this series, the majority of PC subjects (61%) were treated, as a primary treatment, with ADT and therefore a TRT-associated PSA rise was not surprising.

In conclusion, the number of reported cases is still small and heterogeneous; in the absence of randomized controlled trials, the concept of using TRT for PC survivors is still debatable. Current recommendations, including those of the major Andrology Societies, suggest limiting TRT to symptomatic hypogonadal men successfully treated for PC, after a prudent interval, the length of which, however, was not specified.

Complications of ADT

It is well known that, in the male, androgens are essential for the regulation of different bodily functions including sexual response, fat distribution, insulin sensitivity, lipid and bone metabolism, and overall cardiovascular (CV) health. Recent publications highlighted the concept that ADT may result in unfavorable side effects, including increased overall CV morbidity and mortality. The evidence supporting this notion will be better addressed in the following sections.

Androgens and sexual function

The relationship between T and erectile function has not been completely clarified. Experimental studies in animals and human cell cultures indicate that T controls, directly or indirectly, several mechanisms leading to erection and detumescence. First of all, it controls the commitment of penile cells toward a smooth muscle phenotype favoring the functional and structural integrity necessary for penile erection. In addition, T controls numerous enzymatic activities within the corpora cavernosa. In particular, evidence has proven that T positively regulates nitric oxide (NO) formation (acting on endothelial and/or neuronal NO synthase, NOS) and negatively controls the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK). However, the same experimental models have also shown that T regulates the expression of phosphodiesterase type 5. Since T positively controls both the enzymatic steps necessary for initiation (positive effect on NOS and negative on RhoA/ROCK) and termination (positive on PDE5) of the erectile process, its net effect on erection ends up as modest overall. Erections are indeed still possible in hypogonadal conditions, where a decreased cyclic guanosine monophosphate (cGMP) formation, due to impaired NO production, is most probably counterbalanced by reduced PDE5 activity and cGMP hydrolysis. The main physiological action of T is therefore to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections with sex. Accordingly, sexual thoughts and motivations are universally accepted as the most T-dependent aspects of male sexual behavior. For all the aforementioned reasons, treating hypogonadism restores impaired penile erections in experimental animal models, as well as in a clinical setting. Conversely, T administration to otherwise eugonadal individuals is rather ineffective. In line with this evidence, the meta-analysis of placebo-controlled clinical trials indicated that, in comparison to placebo, a significant but moderate improvement of all aspects of sexual function was found in the studies of middle-aged and elderly men with low T (T concentration <12 nmol/L, 346 ng/dl). Interestingly, the meta-regression analysis demonstrated that the effect of TRT on erectile function was inversely related to the baseline T concentration. Hence, the more severe the hypogonadism, the more significant or impressive are the results obtained with TRT. Conversely, no effect was observed for baseline T levels higher than 12 nmol/L.

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Testosterone controls different molecular mechanisms regulating the erectile process:

- The commitment of penile cells toward a smooth muscle phenotype;
- Positively regulates NO formation acting on eNOS and nNOS;
- Negatively controls the activity of RhoA/ROCK;
- Regulates the expression of PDE5.

T net effect on erection is modest.

- The main physiological action of T is to finalize erections with sex.

ADT and sexual dysfunction

Overall it is has been reported that sexual dysfunction, and in particular loss of libido, is the rule in men receiving ADT, with under 20% maintaining any sexual activity. Hence, adequate counseling should be offered to men and their partner prior to recommending ADT. In fact, although PDE5 inhibitors can be theoretically used in the case of ED, their efficacy is usually small in hypogonadal conditions, due to the effect of T on PDE5 gene expression and activity. As previously reported, clinical evidence has demonstrated that long-term ADT clearly improves disease-free or overall survival only in men with locally advanced or high-risk disease. However, this gain is associated with a significant decrease in quality of life. Faced with this scenario, recent studies have revealed that patients with PC are willing to accept an increased risk of death to achieve a better quality of life. Hence an accurate evaluation of the risk/benefit ratio, including the specific possible sex-related adverse events, must be taken in account before prescribing ADT in PC.

CAUTION

Sexual dysfunction occurs very often during ADT.

Some patients with PC are willing to accept an increased risk of death to achieve a better quality of life.

An accurate evaluation of the risk/benefit ratio, including the specific possible sex-related adverse events, must be taken in account before prescribing ADT in PC.

Androgens and bone homeostasis

The specific role of androgens in regulating bone homeostasis is controversial. Data from the generation of AR knockout (ARKO) mice showed that bone volumes are lower in ARKO mice than in both female and male wild-type (WT) litter mates. In addition, in the same animal model the number of osteoclasts in the femoral metaphyses is higher than in WT mice. Similarly, it has been reported that subjects with complete androgen insensitivity due to AR mutations have significantly decreased bone mineral density (BMD) in the spine and hip, when compared with normal subjects and patients with 5α-reductase-2 deficiency. Taking together these data indicates that in the absence of AR, both mice and humans develop osteopenia. Data from epidemiological studies have documented that T plays a crucial role in the maintenance of bone health, both in women and in men, mainly through its aromatization to estradiol (E_2). In particular, data from the European Male Aging Study (EMAS), a large population-based study involving more than 3,000 male subjects aged 40–79 years and recruited from 8 European centers, showed higher total and free E_2, but not T, were independently associated with higher calcaneal quantitative ultrasound. Accordingly, the Framingham Study indicated that in elderly men, serum E_2, but not T, was associated with hip fracture risk. In apparent contrast with these figures, 2 recent studies have reported an association between serum free or bioavailable T levels and the risk of bone fractures, suggesting a possible direct role of T in increasing bone health. Interestingly, in the early studies, serum T levels were measured using immunoassay-based methods, that have been shown to be unreliable, particularly in the lower concentration range (position statement endocrine society). Conversely, the 2 latter studies applied the liquid chromatography tandem mass spectrometry method, the gold standard method for the measurement of steroid hormones. Besides its direct effect, reduced T might also have indirect effects on risk of bone fracture by leading to a reduction of muscle mass, thereby potentially

contributing to fracture risk via impaired balance and increased risk of falls.

The 2 longer studies (up to 36 months of follow-up) evaluating the effect of TRT on bone parameters, showed that T was associated with an increase of lumbar spine and hip bone density. Accordingly, 2 different meta-analyses related to TRT and bone have shown that TRT in comparison with placebo was associated with a reduction of bone resorption markers as well as with an increase of lumbar mineral density. Conversely, insufficient data have been published so far to calculate the effect of TRT on the risk of bone fractures.

SCIENCE REVISITED

- Testosterone plays an important role in regulating bone homeostasis, both directly and indirectly, through its conversion to estradiol;
- TRT is associated with an increase of lumbar spine and hip bone mineral density;
- Insufficient data have been published to calculate the effect of TRT on the risk of bone fractures;

ADT and osteoporosis/bone fractures

In line with the previous evidence, it has been reported that BMD in the hip and spine reduces approximately 3% per year during ADT. Consistent epidemiological data can be derived from the database of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), a collection of records of 50,613 men who have received a diagnosis of PC in the period from 1992 through 1997. Among men who survived at least 5 years after diagnosis, 19.4% of those who received ADT had a bone fracture at any site, as compared with 12.6% who did not receive ADT ($p<0.001$). In addition, the relative risk of the occurrence of any fracture or a fracture that resulted in hospitalization increased with the increasing number of doses of gonadotropin-releasing hormone agonist received. In line with this evidence, a recent meta-analysis of the available studies has documented that PC patients treated with ADT had a 30% higher risk of osteoporosis and 17% higher risk of fracture when compared with patients not subjected to ADT. In addition, the duration of ADT was negatively correlated with lumbar spine and total hip BMD. Conversely, patients with PC had similar levels of BMD and lower rates of osteoporosis in comparison to healthy controls, confuting the general idea that PC patients have lower BMD and higher risk of osteoporosis even before ADT, as a result of age, underlying diseases, or other co-morbidities.

Androgens and glycometabolic control

Some epidemiological evidence suggests that androgens play an essential role in regulating fat mass and insulin sensibility. Figure 5.3 shows the association between androgens and obesity in a large series of subjects attending our unit between 2000 and 2010 seeking medical care for sexual dysfunction. Even though the obesity-associated SHBG decline (Figure 5.3, Panel A) might partially explain the observed fall in T levels (age-adjusted $r=-0.266$; $p<0.0001$), it is important to note that an increased BMI was associated both with lower total and calculated free-T (age-adjusted $r=-0{,}296$ and -0.188, for total and calculated free-T, respectively; both $p<0.0001$, Figure 5.3, panels B and C). Hence, a decline in both SHBG-bound and -unbound T is associated with obesity. An important observation is that LH levels did not significantly rise in obese subjects to compensate the obesity-induced T decline and even tended to decrease as a function of obesity class, after adjusting for age ($p=NS$; see Figure 5.3, panel D). This finding suggests the existence of a functional obesity-related hypogonadotropic hypogonadism and is in keeping with previous data from morbidly

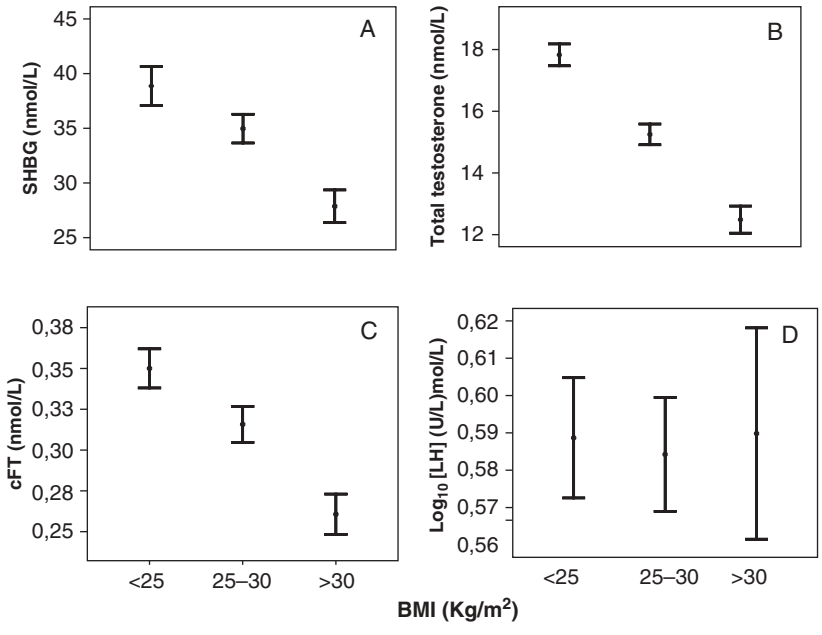


Figure 5.3. Hormonal parameters as a function of obesity classification. SHBG sex hormone binding globulin; T = testosterone; c-free-T = calculated free testosterone according to Vermuelen formula; LH = luteinizing-hormone; BMI = body mass index. Data were derived from a consecutive series of 1,446 patients attending our Unit seeking medical care for sexual dysfunction. Data are expressed as mean (95% confidence interval). All $p < 0.0001$ at ANOVA, except for LH.

obese men, indicating that LH levels and pulse amplitude were attenuated as compared to normal weight controls.

The specific pathogenetic mechanisms linking hypogonadism with obesity and insulin resistance appear to be complex and often multi-directional. Visceral obesity can probably be considered a relevant cause of hypogonadism but at the same time, hypogonadism could be a cause of obesity and insulin resistance, consequently establishing a vicious cycle. Our group recently demonstrated in a rabbit model that experimental metabolic syndrome (MetS; high fat diet) induced hypogonadotropic hypogonadism, and that experimental hypogonadotropic hypogonadism (LHRH analog) induced a dramatic increase in visceral adiposity. Accordingly, in 2 different meta-analyses of available cross-sectional studies, we found that T was significantly lower in subjects with MetS as well as in those with type 2 diabetes (T2DM), when compared to normal subjects. In addition, baseline total T was significantly lower among patients with incident MetS and T2DM in comparison to controls. On the other hand, data derived from the Massachusetts Male Aging Study demonstrated that men who were consistently obese during 8–9 years of follow-up had a greater decline of both total and free T levels. In addition, lifestyle modifications leading to weight loss are characterized by an improvement of cardiovascular profile, as well as by an increase in testosterone circulating levels.

Which molecule plays the major role in this vicious cycle is still unknown but reasonable candidates are estrogens, insulin, leptin, tumor necrosis factor α (TNFα), or other adipokines.

Concerning the effect of TRT on metabolic parameters, a meta-analysis of the placebo-controlled studies performed in middle-aged men showed that TRT is able to reduce fat mass and total cholesterol. Similarly, a meta-analysis evaluating the effects of intramuscular TRT in hypogonadal men, showed a small dose-dependent decrease in total cholesterol and low-density lipoprotein (LDL) and high-density lipoprotein-cholesterol. Very few randomized clinical trials (RCTs) have evaluated the impact of TRT in patients with MetS and T2DM. In patients with MetS, TRT was associated with a significant reduction of fasting plasma glucose, homeostasis model assessment (HOMA) index, triglycerides, and waist circumference, as well as with an increase of HDL-cholesterol. Similar results were observed when T2DM was considered. In particular, TRT was associated with a significant reduction of fasting plasma glucose, HbA1c, fat mass, and triglycerides.

SCIENCE REVISITED

- Pathogenetic mechanisms linking hypogonadism with obesity and insulin resistance appear to be complex and multi-directional: visceral obesity can cause hypogonadism, but hypogonadism could be a cause of obesity and insulin resistance, consequently establishing a vicious cycle.
- The specific molecules involved in this vicious cycle are still unknown, but reasonable candidates are estrogens, insulin, leptin, tumor necrosis factor a (TNFa), or other adipokines.

ADT and obesity

Both cross-sectional and longitudinal studies have demonstrated that ADT increases fat mass and decreases lean body mass in men with PC. Sarcopenic obesity is a relatively new term for the combination of excess weight and reduced muscle mass or strength. Interestingly, these changes appear to be evident even after a short-term (3 months) treatment leading to a reduction of about 2.7–3.8% in lean body mass and to an increase of 6.6–11% in fat mass at 12 months. Several large prospective epidemiological investigations, including the Framingham, the National Health and Nutrition Examination Survey (NHANES), and Prospective Cardiovascular Münster (PROCAM) studies have clearly demonstrated that overweight and obesity are independent risk factors associated with increased mortality in men and that this is due largely to coronary atherosclerosis or other cardiovascular diseases. Hence, ADT-associated obesity might contribute to the increase of CV risk observed in patients with advanced PC treated with androgen suppression.

The best strategy to prevent the ADT-induced adverse changes in body composition is unknown. However, recent evidence has confirmed that, even in PC patients, healthy behaviors, including a balanced diet full of vegetables and fruit, moderated alcohol consumption, and increased physical activity (at least 30 minutes of brisk walking 3 to 5 times per week) are able to minimize differences in fat distribution.

ADT and insulin resistance/diabetes

Insulin resistance is a metabolic abnormality that accompanies diabetes, prediabetes, and obesity. It is an independent risk factor for CV diseases and is present in about a fourth of adults in the general population. Short-term ADT (3–6 months) is associated with an increase of insulin circulating levels, without any significant modification of fasting glucose. The results of these studies suggest that insulin resistance develops within a few months of starting ADT; however, the resulting hyperinsulinemia is adequate to maintain euglycemia. Later, persistent hyperinsulinemia and insulin resistance might lead to the development of T2DM. Accordingly, data from SEER

and the Medicare database, a collection of uniform records from 73,196 men diagnosed with local or local regional PC between 1992 and 1999, demonstrated a significant increased risk of incident diabetes in men treated with ADT. Overall, 36.3% of men received LHRH agonist and 6.9% of men underwent bilateral orchiectomy. Both LHRH therapy and orchiectomy were associated with an increased risk of forthcoming diabetes (44 and 34% increased risk, respectively)

ADT and dyslipidaemia

Conflicting results have been reported on this topic. In fact, although different studies have documented that ADT in men with PC is associated with an increase of total and LDL-cholesterol and triglycerides, one report does not show any change in lipids after 3 months of ADT. Similarly to that which has been observed with glucose modification, the majority of the studies showed that the adverse effects on serum lipids developed within the first 3 months of ADT. Since HDL-cholesterol also increased in some studies, its contribution to cardiovascular risk in men treated with ADT remains unclear.

Testosterone and CV risk

The possible relationship between hypogonadism and CV risk is under intense debate. Low T has been associated with an increased mortality in patients affected by specific diseases, such as hypopituitarism, Klinefelter's syndrome, mental retardation, and in specific populations, such as veterans and Japanese men, with at least one cardiovascular factor. However, studies performed in community-dwelling males have provided conflicting results. In particular, some authors did not report any association between T levels and CV morbidity, after adjusting for confounders, whereas data from the Health In Men Study, a population-based study including 3,620 men aged 70–88 years, suggested a strong relationship between low to normal levels of total T and incidence of cerebrovascular events. In the same study, overt low T levels (total T <8 nmol/L) were not significantly related to incidence of TIA and stroke. Concerning the role of T levels on overall and cause-specific mortality, 2 long-term (>12 years) population-based studies have not shown any significant association between low total T and major cardiovascular event (MACE) mortality. Conversely, data from the European Prospective Investigation into Cancer in Norfolk prospective study, a prospective, population-based survey of 794 men aged 50–91 years, suggested an inverse relationship between serum total T and all cause mortality and MACE.

Similar results have been more recently reported in the Rancho Bernardo Study, in the population-based Study of Health in Pomerania, and in the Third National Health and Nutrition Examination Survey. Our data are in line with the previous findings. We recently reported results from an observational prospective cohort study, involving a consecutive series of almost 1,700 ED subjects, with an 8-year follow-up. In the preliminary analysis of our data, we found that low T, even in the overt hypogonadal range (<8 nmoles/L), was not predictive of MACE, while we described a clear-cut association between overt hypogonadism and/or hypogonadal symptoms and MACE lethality. However, in subsequent evaluation we found that BMI played a crucial role in the stratification of hypogonadism-associated CV risk. In particular, we found a positive association between forthcoming MACE and reduced T levels in normal weight and overweight subjects, which was lost when obese (BMI >30 kg/m^2) patients were considered. Hence, while low T could contribute to the pathogenesis of CV diseases, the reverse is also possible. It can be speculated that obesity-associated hypogonadism is an adaptive mechanism. In fact, we cannot exclude the possibility that low T, as observed in obesity or other chronic diseases, has a protective role by turning off T-dependent functions (i.e. reproduction and physical

labor), that are not desirable when the physical condition is ailing.

The molecular mechanisms underlying the epidemiological associations of low T with CV diseases are complex and not fully understood. As reported above, several cross-sectional studies have reported a direct correlation between T concentrations and more favorable CV disease risk factor profiles, including higher HDL, lower triglyceride concentration, blood glucose, blood pressure, and BMI. In addition, both clinical and animal evidence shows that T exerts a favorable effect upon vascular reactivity, inflammation, cytokine production, and adhesion molecule expressions, as well as on serum lipid concentration and haemostatic factors.

SCIENCE REVISITED

- Epidemiological studies have suggested an association between low T levels and CV mortality.
- Conflicting results have been reported regarding a possible association between low T and incident CV diseases.
- Pathogenetic mechanisms linking hypogonadism with CV risk include a T favorable effect upon vascular reactivity, inflammation, cytokine production, and adhesion molecule expressions, as well as on insulin resistance, serum lipid concentration, and haemostatic factors.
- The possibility that low T, as observed in high-risk CV patients, has a protective role by turning off T-dependent functions (i.e. reproduction and physical labor), that are not desirable when the physical condition is ailing, cannot be excluded.

ADT and increased cardiovascular risk

Data derived from PC patients treated with ADT further complicate the discussion. Some, but not all, studies have reported an association between ADT and forthcoming CV diseases (CVD). Two population-based studies, using data from the SEER-Medicare dataset, reported that ADT is significantly associated with a greater incidence of CV diseases. In the first report, ADT significantly increased the risk of incident coronary heart diseases (HR=1.16), myocardial infarction (HR=1.11), and sudden cardiac death or life-threatening ventricular arrhythmia (HR=1.16). Interestingly, an increased risk of coronary heart disease was evident after 1 to 4 months of treatment. In the second report, ADT caused a 20% increased risk of CVD over 5 years of follow-up. The pooled data from 3 randomized PC trials showed that men 65 years old or older treated with ADT for at least 6 months had shorter times to fatal myocardial infarction (MI) when compared to age-matched men not receiving ADT or younger individuals. Furthermore, evidence from the Cancer of Prostate Strategic Urologic Research Endeavour (CaPSURE) database on almost 5,000 patients revealed that men receiving ADT appear to be associated with an increased risk of death (HR = 2.6) from cardiovascular diseases over a median follow-up of 3.8 years.

In contrast with the aforementioned reports, 4 other *post hoc* analyses of randomized clinical trials reported no associations between ADT and cardiovascular mortality. In particular, 3 large Radiation Therapy Oncology Group (RTOG) trials involving a total of almost 3,000 men with PC have shown comparable CV mortality regardless of ADT assignment. In addition, the European Organization for Research and Treatment of Cancer trial enrolling 985 men with PC not suitable for local treatment did not show any difference in cardiovascular mortality based on timing of ADT.

Differences in patient population studied, study design, selection bias in men offered ADT, and the limited number of CV events in some studies can all be taken into account to explain the discordant observations regarding the association between ADT and cardiovascular mortality. In addition, recent reports have emphasized the concept that ADT might adversely affect CV morbidity and mortality, particularly in men with pre-existing co-morbid CV illness.

Table 5.1. Management of subjects with CV risk factors. Therapeutic strategies for the management of CV risk factors (adapted from Foresta C, Caretta N, Corona G, *et al*. Clinical and metabolic evaluation of subjects with erectile dysfunction: a review with a proposal flowchart. *International Journal of Andrology*. 32:198–211, 2009.

Risk factors 10-yr risk for coronary heart disease	Lower-to-moderate risk (<10%)	Moderately high risk (10–29%)	High risk (>20%)
MetS as a whole	Reduce lifetime risk for ASCVD and diabetes	Reduce both lifetime and short-term risk	Reduce short-term risk
Obesity	10% reduction in body weight (preference for lifestyle therapy) BMI <25%	10% reduction in body weight (consider weight loss drugs) BMI <25%)	10% reduction in body weight (consider weight loss drugs) BMI <25%
Atherogenic dyslipidemia (LDL cholesterol, non-HDL cholesterol)	LDL cholesterol (non-HDL cholesterol) <130 (160) mg/dl <100 (130) mg/dl (with lifestyle)	LDL cholesterol (non-HDL cholesterol) <130 (160) mg/dl (with drugs if necessary) <100 (130) mg/dl (with lifestyle)	LDL cholesterol (non-HDL cholesterol) <100 (130) mg/dl <70 (100) mg/dl (in CHD patients)
Atherogenic dyslipedemia: HDL cholesterol	Raise HDL (lifestyle therapy)	Raise HDL (lifestyle therapy)	Raise HDL (lifestyle therapy)
BP	BP = 140/90 mmHg (with drugs if necessary) 130/80 (with lifestyle therapy)	BP = 140/90 mmHg (with drugs if necessary) 130/80 (with lifestyle therapy)	BP = 140/90 mmHg (with drugs if necessary) 130/80 (with drugs in diabetes and chronic renal failures
Elevated FBG (prediabetes)	FBH <100 mg/dl (with lifestyle therapy)	FBH <100 mg/dl (with lifestyle therapy)	FBG <100 mg/dl (consider indulin sensitizer)
Elevated FBG diabetes	HbA1c 6–7%	HbA1c 6–7%	HbA1c 6–7%
Prothrombotic state	No drugs	Consider antiplatelet drug	Antiplatelet drug
Proinflammatory state	Complete smoking cessation	Complete smoking cessation	Complete smoking cessation

BP - blood pressure; FBG - fasting blood glucose.

Cardiovascular evaluation and management of patients treated with ADT

In light of the aforementioned evidence, the American Heart Association, American Cancer Society, and American Urological Associations, in a common position statement, recently recognized that ADT adversely affects traditional CV risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Accordingly, a possible relationship between ADT and CV events and death has been recognized. However, the same consensus emphasised the concept that, at present, there are no specific tests or examinations to stratify CV risk before

starting ADT. For all patients, and particularly those with CV disease, the prescribing physician should weigh the risk/benefit ratio of ADT. Prudence and good medical care should guide appropriate preventive measures (Table 5.1).

These should generally include behavioral changes such as smoking cessation, moderate alcohol consumption, and diet full of fruits and vegetables. In addition, statin therapy should be offered to maintain LDL levels lower than 100 or 70 mg/dl, based on cardiovascular risk; adequate antihypertensive, and glucose therapies should be prescribed, whenever appropriate, in order to obtain optimal blood-pressure and glycaemic control. Finally, all patients with CV should be taking aspirin unless there is a strong contraindication. Patient evaluation should include the assessment of blood pressure, waist circumference, lipid profile, and glucose levels. Given that some of the effects of ADT occur within the first 3 months of treatment, the initial follow-up should occur within 3 to 6 months after initiation of therapy and at least yearly thereafter.

☆ TIPS & TRICKS

CV evaluation of patient treated with ADT must include at 3 to 6 months and at least yearly thereafter: blood pressure, waist circumference, lipid profile, and glucose levels.

CV management of patients treated with ADT must include behavioral changes:

- smoking cessation
- moderate alcohol consumption
- diet full of fruits and vegetables

Specific treatments:

- Statin therapy to maintain LDL < 100 or 70 mg/dl based on CV risk
- Adequate antihypertensive and glucose therapies, whenever appropriate
- Aspirin, unless contraindicated.

Conclusions

Androgens play an essential role in the development and differentiation of the prostate gland, although their contribution to pathological conditions, such as BPH and PC, remains unclear. Clinical data indicate that prostate androgen dependency is evident only in the hypogonadal condition (the "saturation hypothesis"). ADT is the cornerstone in the treatment of advanced and metastatic PC, reducing PC growth and patient symptoms. There is clear evidence that ADT improves disease-free and overall survival only under particular conditions. In addition, since androgens are essential for the regulation of different bodily functions, including fat distribution, insulin sensitivity, and lipid and bone metabolism, recent publications highlighted the concept that ADT may also be involved with increased overall and cardiovascular morbidity and mortality. Hence, while ADT still represents a cornerstone for the palliative therapy of a small fraction of aggressive PC, a "misuse and/or abuse" of ADT should be avoided. Physicians should weigh the risk/benefit ratio before prescribing ADT.

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6

Hormonal Regulation of Male Sexual Desire: the Role of Testosterone, Estrogen, Prolactin, Oxytocin, Vasopressin, and Others

Antonio R Granata, Valeria Pugni, Vincenzo Rochira, Lucia Zirilli, and Cesare Carani

University of Modena and Reggio Emilia, Baggiovara (Modena), Italy

Introduction

Sexual appetitive function may be divided in sexual desire and sexual arousal; these 2 components are at least in part overlapping and closely related to each other (Bancroft 1989; Pfaus 209). Sexual desire may be defined as both the natural occurrence of sexual thoughts and the biological need for sexual activity (including also the interest in sexual objects or experiences). The terms libido, sexual interest, and sexual appetite are often used as synonymous of sexual desire, which results from a complex interaction among cognitive processes (thoughts and imaging), neurophysiological mechanisms (central arousability), and affective components (mood and emotional states). In fact, both external (visual, olfactory, auditory, and tactile) and internal (thoughts, ideas, imagination, emotions, and fantasies) stimuli contribute to sexual desire initiation, maintenance, and amplification. Libido in humans is related also to gender identity and sexual preference (Bancroft 1989; Pfaus 209).

Sexual desire should not be confused with sexual arousal, which might be looked at as the consequence of sexual desire itself. Sexual arousal consists of psychological and physiological changes, which occur when a person is sexually excited; these changes are self-amplified: the response in preparation for

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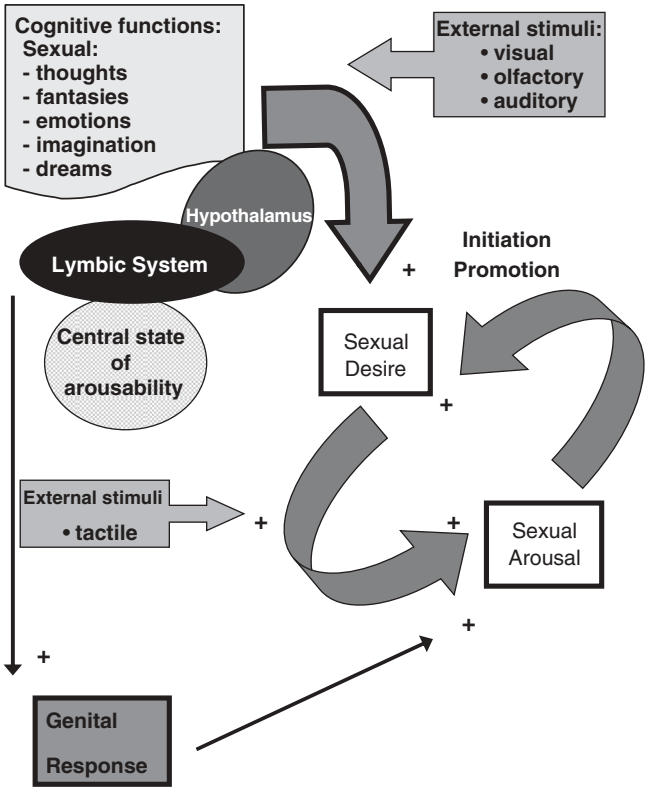


Figure 6.1. Schematic representation of mechanisms involved in sexual desire and arousal initiation, maintenance, and amplification.

sexual activity facilitates sensitivity with a consequent escalation of arousal. Intimately connected with sexual desire, sexual arousal is defined in either subjective or objective terms. In subjective terms, the sexual arousal has psychological components (e.g. feeling sexually excited); in objective terms, the sexual arousal shows physical changes (e.g. genital vasocongestion) (Meston 2000). In addiction, central arousability (degree of intrinsic arousability) is involved in determining the individual's reactivity to sexual stimuli, thus it may be considered the neurophysiological substrate of male sexuality and modulates the sexual response (Figure 6.1).

However, according to some authors, whether desire and arousal in men can be reliably differentiated is still controversial (Pfaus 2009).

☆ TIPS & TRICKS

Sexual desire should not be confused with sexual arousal:

- *Sexual desire* is both the naturally occurrence of sexual thoughts and the biological need of sexual activity.
- *Sexual arousal* is the consequence of sexual desire and consists of psychological and physiological changes, which occur when a person is sexually excited.

There is no objective physiological criterion to evaluate both sexual desire and sexual arousal in men, therefore desire and arousal are measured from self-reported questionnaires, whose results are strongly dependent on external factors (psychological and subjective

Table 6.1. Appetitive sexual behavior and a parallelism of its measurement between men and male rodents

Appetitive sexual functions	Components in men	Measurement in Humans	Measurement in Animals
Sexual desire or sexual interest (libido)	– Cognitive processes – Neurophysiological mechanisms (central arousability)	Cognitive parameters. Frequency of sexual: – thoughts – fantasies – dreams – wishes	Motivational component: – all initiation behavior that anticipates sexual activity (active pursuit of the female, partner's sniff and nuzzling)
	– Affective components (emotions)	Behavioral parameters	
Sexual arousal	The perception of own sexual excitement (subjective) and consciousness of physiological changes during excitement (objective)	Frequency of sexual activity: – intercourse – masturbation – sleep erections	– latency to mount – latency to first intromission
		Psychological parameters: – erectile response to erotic stimuli	Copulatory component: – post-ejaculatory interval

state) (Meston 2000; Pfaus 2009) (Table 6.1). Efforts have been made to extrapolate useful information from animal behavior, in order to obtain objective data concerning the physiology of human sexual function. For an adequate comparison of the sexual desire mechanisms between animals and humans, some behavioral parameters of sexual initiation have been identified in rodents, in which sexual behavior may be differentiated into a sexual motivational component and in a copulatory component (Meston 2000; Pfaus 2009), with the motivational component corresponding to what would be arousal in humans (Everitt and Bancroft 1991). The motivational component can be measured by the analysis of precopulatory activities and by the latencies to copulatory behavior. The precopulatory activities consist of anogenital sniffing, nuzzling, active pursuit of a partner, and partner preference; the parameters of the latencies to copulatory behavior consist of mounting, intromission, and post-ejaculatory interval (Table 6.1).

Bearing in mind the differences between sexual desire and sexual arousal in men, the research has not yet been exhaustive in detecting their mechanisms.

Central control of sexual desire

In male rodents, the areas of the brain mainly involved in the control of reproductive behavior are the medial preoptic area (MPOA), the ventral medial nucleus (VNM) in the hypothalamus, and limbic system (Maisel and Sachs 1994) (Figure 6.1).

Traditionally, the limbic system is considered the neural substrate for several

Table 6.2a. Mechanisms of action of sexual steroids on male sexual behavior

Sex steroids	Source	Action
ANDROGENS Testosterone DHT	Circulating sex steroids Locally produced sex steroids	– Endocrine – Paracrine – Autocrine
ESTROGENS Estradiol Estrone Estriol		
Type of action	Mechanism	Effect
Genomic actions	Nuclear receptor	Slow effects: modulation of gene expression
Non-genomic actions	Cell membrane receptor	Rapid effects: changes in iones transport

appetitive functions, which also include sexuality, in both humans and animals. Several evidences and experimental studies support this concept. In male rhesus monkeys, studies based on external stimulations or lesions of several areas of the central nervous system revealed a number of brain sites (MPOA, VNM, and limbic system) involved in the promotion and/or initiation of sexual activity. The MPOA seems to be specifically involved in the initiation of copulatory behavior; in the animal model, this activity is considered to correspond to sexual desire in the human male. Cross-species comparative studies suggest that hypothalamus and limbic system areas also have an important role in humans for male sexual appetitive behavior, as recently confirmed by studies of men based on positron emission tomography (Redoute *et al.* 2000) (Figure 6.1).

SCIENCE REVISITED

According to cross-species comparative studies and to positron emission tomography, the hypothalamus (medial pre-optic area and the ventral medial nucleus) and the limbic system are involved in the control of sexual behavior.

Sex steroids

The role of the hypothalamus and limbic system in male sexual behavior is suggested by the local production of sex steroids and by the presence of their receptors (Roselli 1991). Sexual desire in humans is at least in part dependent on circulating and locally produced sex steroids (Table 6.2a).

In both animals and humans, the effects of sex steroids on sexuality are of 2 kinds: organizational or activational (Bancroft 1989) (Table 6.2b).

Organizational effects occur in a definite period during early development and lead to permanent effects on sexual behavior, which also persist when sex steroids are absent. A sex steroid-dependent neuron arrangement during early development leads to the establishment of a male human brain, which is the prerequisite for normal male adult sexual behavior; therefore the effect of sex steroids in the early phase of life has a role on both sexual desire, sexual arousal, and probably on sexual preferences in adult life.

Conversely, activational effects of sex steroids are directly exerted during adulthood and they mainly consist of facilitating both sexual desire and sexual activity. Thus, a continuative presence of circulating or locally produced hormones is required to

Table 6.2b. Sex steroids activity on male sexual behavior

Type of sex steroid action on male sexual behavior	Mechanisms	Duration	Final effects
Organizational *Genomic events*	Neuron organization in a male brain during prenatal and perinatal period	*Permanent effects*	Prerequisite for the establishment of a male sexual brain
Activational Genomic or Non-genomic events	Modulation of cellular functions, which are dependent on steroid presence	Temporary effects	Facilitating and maintaining effects on sexual desire and activity

ensure the occurrence of activational effects. Activational effects (sexual interest and activity) disappear in the absence of gonadal hormones, as it happens in castrated animals or hypogonadal men, and they are restored by testosterone replacement treatment (Maisel and Sachs 1994).

Androgens

Nowadays, androgens are generally accepted by physicians as the major determinant in male reproductive function.

Direct androgen action is exerted mainly by testosterone and its metabolites, particularly dihydrotestosterone (DHT). The mechanisms of action of androgens on sexual behavior are summarized in Tables 6.2a and 6.2b. The organizational actions of androgens on the brain are mediated by their aromatization into estrogens. Furthermore, the androgens regulate the activity of the enzyme aromatase in several brain areas (Rochira *et al*. 2002). The stimulation of reproductive behavior is one of the best-known activational effects of testosterone on the central nervous system of adult men (Fernandez-Guasti *et al*. 2000; Rochira *et al*. 2002). Activational effects start at puberty concomitantly with the behavior of testosterone levels, which modulates male sexual behavior and determines the starting of sexual thoughts and fantasies (Table 6.2b).

Animal studies

Studies on orchiectomized animals are the basis for understanding the dependence of copulatory behavior of male rats on androgens (Bancroft 1989). The castration of male rats leads to a reduction of sexual interest until its complete disappearance, an event that also occurs in several species, including primates (Pfaus 2009). In male rats, the negative effects (decrease in the number of male mountings, intromissions and ejaculations, increase in intromission latency, mount latency, and post-ejaculatory interval) are closely related to the time since the castration was performed ({Pfaus 2009).

In conclusion, androgens facilitate initiation and promotion of both sexual interest and arousal in rats.

Human studies

Male sexual behavior in adult mammals is mostly modulated by testosterone, and androgens are required for a normal sexual activity in adult men (Robbins 1996).

The relationship between serum testosterone levels and male sexual behavior is still not completely clear, but in hypogonadal or castrated men, very low serum testosterone levels are almost constantly associated with a decrease in sexual interest and sometimes with erectile dysfunction. Subjective quality of sexual acts, sexual excitement,

and frequency of both sexual thoughts and sexual activity are impaired in hypogonadal men, and are restored by testosterone replacement (Carani *et al.* 1996).

In adolescent boys, free testosterone serum levels are directly related to the frequency of sexual thoughts, as well as with the initiation and rate of sexual intercourse (Halpern *et al.* 1994).

The individual variability in testosterone levels in normal adult men, as well as exogenous supraphysiological amounts of testosterone, does not modify sexual interest or behavior (Carani *et al.* 1996). A recent study shows testosterone to have significant positive effects on sexual desire only among men with abnormally low testosterone levels, confirming that testosterone treatment is efficacious in restoring a normal sexual drive in a dose-dependent fashion only for serum levels lower than normal ranges (Carani *et al.* 1996). By contrast, the withdrawal of testosterone replacement therapy results in a severe impairment of sexual desire after 3–4 weeks of washout (Carani *et al.* 1996). Sleep-related erections and erections in response to visual erotic stimuli are strongly androgen dependent. Androgen replacement therapy restores normal sleep-related erections in hypogonadal men who show impairment of both sleep-related penile rigidity and increase of tumescence (Carani *et al.* 1996). In a recent study we suggested 2 thresholds for serum testosterone levels: one (350 ng/dl), below which sleep related erections are normal and sexual behavior is impaired only in some subjects, and a lower one (150 ng/dl), below which both sleep related erections and sexual behavior are almost constantly impaired (Carani *et al.* 1996).

In conclusion, androgens are necessary though not sufficient for normal sexual desire, and men have probably more testosterone than they need for a full androgen effect on sexuality; therefore, most variations in testosterone levels between the low end and the high end of its normal range would have no effect on sexual behavior.

SCIENCE REVISITED

Testosterone is required for normal sexual activity in adult men.

Very low testosterone levels are associated with constantly impaired sleep-related erections and sexual behavior.

Mild hypotestosteronemia is associated with normal sleep related erections, while sexual behavior is impaired only in some subjects.

Estrogens

In the past, researchers have claimed little direct influence of estrogens on sexual desire in both males and females. The role of estrogens on male sexuality has been partially clarified in mammals, but the relationship between estrogens and sexual behavior still remains unresolved in men (Rochira *et al.* 2002).

The human hypothalamic distribution of the aromatase enzyme shares the same areas of some other species, including rats and primates (Fernandez-Guasti *et al.* 2000), suggesting a local production of estrogens in the brain.

Gender identity and partner preferences are strictly linked with sexual behavior and sexual desire. In non-primate male mammals, androgen exposure in the prenatal/perinatal period (i.e. the organizational phase of the brain) probably accounts for the sexual dimorphism of the central nervous system, as well as for differences in sexual behavior between sexes. Paradoxically, estrogens are mainly involved in the establishment of a male brain in rats, as a consequence of the precocious production of testosterone and its aromatization in male rats, an event that does not occur in females. This masculinization effect of estrogens on the brain of a very young male rat is due to the permeability of the emato-liquoral barrier to sex steroids, which is lower for estrogens and higher for androgens; the higher testosterone serum levels in

the young male rat lead to a high testosterone concentration in the brain and to a subsequent higher estrogen concentration, due to the presence of aromatase in the brain itself (Pilgrim and Reisert 1992).

By contrast, a possible strict linkage among anatomic correlates, early hormonal exposure, and sexual orientation is widely criticized, because of the role exerted by both nurture and environmental factors on behavior in humans (Collaer and Hines 1995).

Recent data from men suggest a minor role of aromatization in the process of sexual orientation. Patients with congenital estrogen deficiency show unaffected sexual orientation and unaffected gender identity, despite the absence of aromatase activity in the brain during early development (Rochira *et al.* 2002), suggesting that in humans, estrogens are not involved on the development of psychosexual orientation and gender identity. Thus, some unresolved questions concerning the supposed relationship between estrogens and sexual orientation in men still remain (Rochira *et al.* 2002). Probably in humans, psychological and social factors are the major determinants of gender role and sexual behavior (Collaer and Hines 1995). Obviously sex steroids are indirectly involved in human psychosexual development, since they act on sexual differentiation, determining both sex assignment at birth and the sex of rearing with consequent reflection on adult sexual behavior and partner preference.

Animal studies

A role for estradiol in male sexual behavior has been clearly demonstrated in rodents. This observation comes from the effect of different androgens in restoring sexual behavior in castrated rats: while testosterone, which is an aromatizable androgen, restores sexual behavior in a castrated animal, non-aromatizable androgens, such as DHT, will not restore sexual behavior in castrated males of many species, and the administration of aromatase inhibitors will also block male sexual behavior (Maisel and Sachs 1994). Therefore, estrogens also have a role in sexual behavior in males, and androgens also exert their action through their aromatization in estrogens.

Recent studies on mice models lacking estrogen receptor α (αERKO), both α and β receptors (αβERKO), and aromatase enzyme (ArKO), showed that parameters of sexual behavior, which constitutes a correlation of human sexual desire, are impaired (Everitt and Bancroft 1991), despite normal to high testosterone serum levels. A prolonged latency to first intromission and mount is common in ArKO and αERKO mice, as well as in αβERKO mice. Conversely, male sexual behavior is normal in βERKO mice (Ogawa *et al.* 1999).

Thus, aromatization of androgens is required to ensure normal male sexual behavior, according to that previously suggested in gonadectomized rats treated with testosterone alone or in combination with the aromatase inhibitor fadrozole (Ogawa *et al.* 1999). Consummatory behavior (intromission and ejaculation) seems to be more severely impaired in the absence of estrogens with respect to motivational behavior, which probably is more sensitive to testosterone. In conclusion, the α-estrogen receptor seems to play a major role in the control of male sexual behavior, even though an involvement of non-nuclear estrogen receptors has been recently suggested (Ogawa *et al.* 1999).

Human studies

Much less is known about the estrogen role in human male sexual behavior, with doubts on how many of the effects of testosterone are due to its conversion into estradiol (Rochira *et al.* 2002). In the past, 2 studies suggested a positive role of estrogens on human male sexual behavior, showing an increase in libido and sexual desire during estrogen treatment. In a double blind study, an improvement of sexual activity, particularly libido and frequency of coitus, was

recorded in a castrated man during treatment with conjugated estrogens plus medroxyprogesterone (Luisi and Franchi 1980). In another double blind comparative study in hypogonadal men, the sexual activity, particularly libido, was more improved during testosterone undecanoate administration than during the administration of the not-aromatizable androgen mesterolone (Luisi and Franchi 1980). Conversely, some clinical studies on normal men lead to opposite results, with sexual function unaffected by the administration of the estrogen receptor antagonist tamoxifen or of the aromatase inhibitor testolactone (Rochira *et al*. 2002). Again, sexual activities in men were not modified by the selective depletion of serum estradiol obtained by using an aromatase inhibitor, if testosterone levels were maintained in the normal range (Rochira *et al*. 2002). In addition, supraphysiological doses of estrogen treatment in male sex offenders can inhibit sexual desire because of the inhibitory effects on gonadotropin and testosterone levels.

In men affected by congenital estrogen deficiency, no remarkable sexual dysfunction was recorded (Rochira *et al*. 2002), suggesting that estrogens are not strictly necessary for a normal sexual behavior in men, even though they may play a role. An estrogen role on human male sexual behavior is suggested by an unexpected improvement of sexual behavior parameters (sexual desire and frequency of sexual activity) during transdermal estradiol treatment in an aromatase-deficient man, while in this subject, sexual activity was not modified by a previous testosterone treatment (Rochira *et al*. 2002).

Despite obvious limits of extrapolation due to difficulties in making a comparison of rodent and human paradigms of sexual behavior (Everitt and Bancroft 1991), the results from men with congenital lack of estrogens theoretically agree at least in part with those obtained from animal studies (Ogawa *et al*. 1999).

☆ TIPS & TRICKS

The literature shows doubts on estrogens role in human male sexual behavior:

- no sexual dysfunction in men affected by congenital estrogen deficiency;
- improvement of sexual desire and frequency of sexual activity during transdermal estradiol treatment in an aromatase-deficient man.

Prolactin

Hyperprolactinemia is usually associated with sexual impairment, which is often corrected once the prolactin levels are reduced.

The precise nature of the prolactin effect is not completely clear, in particular whether sexual interest and/or erectile function is primarily affected. However, in one of our studies (Carani *et al*. 1996), sleep related erections have been found not impaired in hyperprolactinemic men compared with hypogonadal men.

Prolactin has been suggested to have a negative role on sexuality through both a direct and an indirect action. The indirect action on sexuality would consist of inhibiting sex steroid secretion by an excessive endogenous opiate tone, which would inhibit pulsatile release of gonadotropin-releasing hormone (GnRH) through an effect on the hypothalamic median eminence; this, in turn, would reduce the frequency of the luteinizing hormone (LH) release and the ensuing production of testosterone. Prolactin direct action on sexuality could be exerted by a poorly substantiated steroidogenesis inhibition directly in the testes and by an action on the central nervous system; the latter one is suggested by the occurrence of low libido also, when hyperprolactinemia is not associated with hypogonadism (Carani *et al*. 1996).

The main hyperprolactinemia effect could be the reduction of sexual interest as it occurs

in men with low testosterone serum levels. In hyperprolactinemic men, erectile dysfunction is likely to be a psychogenic reaction to the loss of sexual interest and to both the consequent tension and conflicts in the sexual relation.

Oxytocin

Several data suggest that oxytocin has a role on social behavior, both in animals and humans, and is regarded as a "bonding hormone."

For what concerns the effect of oxytocin on sexual behavior, several data are available from animal studies: in male rodents, oxytocin has a positive role in copulatory activity, erectile mechanism, and ejaculation.

The few data available in men suggest increased oxytocin plasma levels, both during sexual arousal and orgasm in men (Lee *et al*. 2009).

Vasopressin

As oxytocin, vasopressin has a positive role on social recognition, bonding behavior, and sexual behavior in animals. Also in men, vasopressin has been recognized as a bonding hormone and very recent data suggest that this hormone is also involved in the enhancement of cognition of sexual stimuli (Guastella 2011).

Dopamine

The data on the dopamine (DA) role in sexual arousal and desire come mainly from animal studies, and from human studies on side effects of the treatment of Parkinson's disease with 3,4-dihydroxy-L-phenylalanine (L-DOPA). DA is associated with 3 major brain systems, which take part in sexual arousal and desire: the diencephalic incertohypotalamic DA system linked with the MPOA of the anterior hypothalamus; the mesolimbic and mesocortical DA system linked with the nucleus accumbens (NAC) and the medial prefrontal cortex; and the nigrostriatal system, linked with the striatum (Pfaus 2009).

MPOA lesions lead to both impaired sexually rewarded maze learning and abolished initiation of copulation in male rats. NAC lesions impair sexual arousal in male rats. In sexually normal male rats, the DA receptor agonist apomorphine stimulates penile erection, but does not influence measures of sexual desire. Quinelorane, a dopamine D2 receptor selective agonist, promotes copulation in sexually inactive male rats and reduces the ejaculatory threshold in sexually active male rats. Appetitive and consummatory sexual behaviors are stimulated by L-DOPA in male rats and these effects are blocked by the DA-receptor antagonist pimozide.

In men on L-DOPA treatment, libido is enhanced, but on the other hand, it is unclear if nausea and vomiting are reported as side effects of apomorphine or L-DOPA (Pfaus 2009).

☆ TIPS & TRICKS

Dopamine acts on sexual arousal and desire through 3 brain systems:

- the diencephalic incertohypotalamic system;
- the mesolimbic and mesocortical system;
- the nigrostriatal system.

Dopamine has a positive role on sexual behavior and measures of sexual desire in male rats.

In men, L-DOPA treatment enhances libido.

Melanocortins

Among the neuropeptides derived from Pro-opiomelanocortin, Adrenocorticotrophic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH) bind to some of the at least 5 types of melanocortin

receptors (MCR); MCR3 and MCR4 are present in the hypothalamic and limbic regions (Pfaus 2009).

The MCR agonists melanotan-II, and its metabolite bremelanotide, stimulate sexual arousal and desire in humans and rats; these 2 substances also stimulate erection in men with and without erectile dysfunction.

It is noteworthy that systemic bremelanotide administration stimulates DA release in MPOA, suggesting that MCRs have a positive role in DA release in MPOA; furthermore, this bremelanotide effect on DA is contrasted by the co-administration of an MCR4 antagonist or a dopamine D1 receptor (D1R) antagonist, with D1R involved in the facilitation of sexual desire.

Conclusions

The activation of incerto-hypotalamic and mesolimbic systems of the brain stimulate both a behavioral pattern and subjective feelings, which are regarded as sexual desire, which becomes libido when genital arousal also occurs.

Several hormones are involved in the cerebral excitatory pathway, in the penile erection, and in the sexual behavior; however, sex steroids, in particular testosterone, have a main role in the male sex drive. Among sex steroids, estrogens are also shown to have an active role on male sexuality, with estrogen physiological levels presumably being required for completely normal sexual behavior in men.

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7

Endocrinology of the Ejaculatory Process (Thyroid Hormones, Prolactin, Oxytocin, Testosterone)

Emmanuele A Jannini[1] and Andrea Lenzi[2]

[1] University of L'Aquila, L'Aquila, Italy

[2] University of Rome "La Sapienza," Rome, Italy

Introduction

Ejaculation is a psycho-neurouroendocrine mechanism. Major progress has been made in the field, and currently a whole host of neurotransmitters, chemical effectors, growth factors, second-messenger molecules, ions, intercellular proteins, and hormones have been characterized as components of the complex physiology of ejaculation. The aim of this chapter is to review the evidence so far produced, regarding the hormonal regulation of the ejaculation.

Neuroanatomical and physiological aspects

Ejaculation is a complex physiologic event resulting from the interactions of the nervous system on highly specialized peripheral organs. This physiological reflex is actually 2 successive co-ordinated processes, emission and expulsion, each of which involves different anatomical structures. The reflex is mediated by a spinal control center, referred to as a spinal ejaculation generator (SEG). This SEG co-ordinates sympathetic, parasympathetic, and motor outflow to induce the 2 phases of ejaculation, i.e. emission and expulsion. In addition, the SEG integrates this outflow with inputs conveying biochemical or mechanical information from the accessory sex organs. In addition, the SEG is under inhibitory and excitatory influence of supraspinal sites. The efferent limb of the reflex, responsible for emission, consists of sympathetic efferent fibers (T_{10}–L_2, called a secretory center) that cause sequential contractions of the epididymis, vas deferens (VD), seminal vesicles (SV), and prostate, with closure of the bladder neck. True ejaculation is then initiated somatically from the sacral spinal cord (S2–S4) via the pudendal nerve, causing rhythmic contractions of the bulbospongiosus and bulbocavernosus muscles and other associated perineal muscles, which force the ejaculate through the distal urethra.

The onset of ejaculation is triggered by sensory inputs to the spinal control center during the sexual activity prior to ejaculation. These sensory inputs may involve somatosensory, visceral sensory, or proprioceptive inputs. The sensory information is then transmitted via the dorsal nerve of the penis

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(S_4) to the lumbosacral spinal cord, and is joined by sympathetic afferents from the hypogastric plexus, conveying biochemical and/or mechanical information from the accessory sex organs. Traveling up the spinal cord (and joined by visual, auditory, and olfactory cerebral afferents), the impulses are integrated by cerebral structures specifically activated during ejaculation, to form a tightly interconnected network comprising hypothalamic, diencephalic, and pontine areas.

The regulation of the ejaculatory reflex requires neurochemically co-ordinated interrelationships at different levels of the neuraxis. Several neurotransmitter systems have been implicated in this process. The central serotonergic and dopaminergic neurons play a primary role; other chemical factors, including acetylcholine (Ach), adrenaline, neuropeptides, oxytocin (OT), gamma-aminobutyric acid (GABA), and nitric oxide (NO), intervene secondarily. We believe that all these transmitters act together to form a balance between excitatory and inhibitory transmission, which is critical for the normal ejaculatory process, while the imbalance caused by disturbing any of these systems can promote either premature ejaculation (PE) or retarded ejaculation. The endocrine system is also intricately involved with the brain and the peripheral organs. Hormones regulate sexual behavior primarily by slow, genomically mediated effects. These effects are realized, in part, by enhancing the processing of relevant sensory stimuli, altering the synthesis, release, and/or receptors for neurotransmitters in integrative areas, and increasing the responsiveness of appropriate motor outputs. OT is another hormone recently involved in the regulation of the mechanism of ejaculation. It has been postulated that both 5-HT and OT might be involved in the etiology of lifelong PE. Although many of the individual pieces of the ejaculatory process have been identified, the manner in which these neuroendocrine systems interconnect to mediate a co-ordinated process has not been well delineated (see Table 7.1 for the effects of different neurotransmitters and hormones on the ejaculatory process).

Definition and pathophysiology of PE

Historically, attempts to explain the etiology of PE have included a diverse range of biological and psychological factors. Most of these proposed factors are, so far, not evidence-based, and are speculative at best. This approach, dichotomizing between biological vs. psychological, or the psychogenic vs. organogenic, is based upon a false premise that incorrectly assumes that psychological processes are somehow independent (and mutually exclusive) of biological events. These factors are not completely independent, as both influences often overlap at the level of the central nervous system. Thus, all cases of PE are or become psychogenic and capable of provoking a psycho-relational imbalance. While it is clear that all behavioral dysfunctions may negatively influence organic processes (psycho-somatic evidence), it is also plain that a disease or a symptom of the body may affect behavior (somato-psychic evidence). Thus, it should be admitted that PE is a psycho-neuro-uro-endocrine disorder affecting the couple. Anyway, several studies have been performed to investigate the etiology and pathogenesis of PE.

The clinical definition of PE is an ongoing process. Recently, the International Society for Sexual Medicine (ISSM) proposed an evidence-based definition for primary LL-PE as:

> a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and, inability to delay ejaculation on all or nearly all vaginal penetrations; and, negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

Table 7.1. Effects of neurotransmitters and hormones on the ejaculatory process

Neurotransmitter/ hormone	Central		Peripheral	
	Effect	Species	Effect	Species
Norepinepherine	Excitatory	Man Rat	Excitatory	Human VD,SV, prostate and urethra
Acetylcholine	Excitatory	Rat	Excitatory No effect	Rat VD Rat and guinea pig prostate Human VD Human VD and prostate
Adenosine triphosphate (ATP)	Not available (NA)	NA	Excitatory Excitatory	Rat and guinea pig VD and prostate gland Human VD
Dopamine	Excitatory	Rat Human	Excitatory	Human VD and prostate
Glutamic acid (glutamate)	Excitatory	Rat	Inhibitory	Rat VD
Gamma Amino Butyric Acid (GABA)	Inhibitory	Rat	Inhibitory	Rat VD (44) Rat ischiocavernosus
Serotonin	Inhibitory Excitatory	– Human – Rats: 5-HT2c agonists – Rat: 5-HT1B agonists – Rat: 5-HT5 2B agonists – Rat : 5-HT1A agonists	Inhibitory Excitatory	Rat VD and SV – Mouse VD : 5-HT1A stimulation
Angiotensin II	Inhibitory	Rat	Excitatory	– Rat VD
Oxytocin	Excitatory	Rat Human	Excitatory No effect	Rat and rabbit : prostatic urethra, bladder neck and ejaculatory duct Rat and Rabbit : VD,SV, epididymis, and prostate
Thyroid hormone	Excitatory	Rat Human	Excitatory	Rat Human
Testosterone	Excitatory	Human	Excitatory	Human
Prolactin	Inhibitory	Human	?	?
Nitric oxide	– Excitatory (MPOA) – No effect (PVN)	Rats –Rats	Inhibitory	Human SV
Vasoactive intestinal peptide (VIP)-	Excitatory	Rat	No effect	Dog
Substance P	Inhibitory	– Rats	Excitatory	Mouse VD
Opioids	– Excitatory (low dose in MPOA) – Inhibitory (high dose in MPOA)	– Rats – Rats	– Complex dual effects (Inhibitory and excitatory). – No effect	– Rat VD – Human VD

Table 7.2. The risk factors for acquired premature ejaculation

Group of diseases	Diseases
Psychorelational	Anxiety, relational, and marital problems
Neurological	Penile hypersensitivity
Endocrine	Hyperthyroidism
Urologic	Prostate inflammation/infection
Other sexual symptoms	Comorbid with erectile dysfunction, hypoactive sexual desire, female sexual dysfunction

Although no logical reasons exist for suspecting substantial differences in intravaginal timing and patient's outcome in patients with LL- and acquired (A-PE) forms, the lack of evidence-based IELT and patient-related outcomes (PRO) have frustrated the efforts to define A-PE, which has been so far simply recognized as a PE occurring after a period of normal ejaculatory control. The obvious inferring of this is that LL-PE is more likely to be sustained by congenital causes, while the acquired form must be grounded on psychological events or organic *noxae* able to affect the complex mechanism of ejaculation. We propose to define A-PE as:

> a male sexual dysfunction occurring after a period of normal ejaculatory performance, in which ejaculation occurs within about 2 minutes after vaginal penetration. The inability to delay ejaculation can be either: i) a possible symptom of neurologic, endocrine, and urological diseases; ii) correlated to psychological difficulties; iii) a co-morbidity with other sexual dysfunctions; or iv) idiopathic.

The pathophysiology of A-PE appears, in fact, to be both neurobiogenic (endocrine, urologic, neurobiologic) and psychogenic. In other words, A-PE is a psycho-neureoendocrine and urological symptom with a possible comorbidity with another sexual disturbance: this means that the A-PE has been correlated to psychological, neurological, hormonal, urological diseases and to other sexual symptoms such as impotence. Endocrine pathology of PE obviously concerns the acquired forms.

Exactly as for the psychological causes of PE, no one of the neurological, endocrine, and urological pathologies listed in literature has been demonstrated to be a direct cause of A-PE. All these must be considered, at the best, pathological conditions associated with PE deserving medical attention and treatment in order to maximize the therapeutic efforts of the symptom PE. In other words, the best way to consider the candidate aetiologies of A-PE here listed is to regard them as organic risk factors for A-PE (Table 7.2).

Endocrine risk factors of PE

From the previous paragraphs, it appears evident that hormones play a central role in the machinery of emission-ejaculation; this implies that pathological hormonal levels may directly or indirectly affect the ejaculatory control, as in the case of the thyroid hormone, but may be also be affected or simply modified by the condition of PE. This seems to be the case of testosterone and prolactin levels in A-PE.

The role of sex steroids

Testosterone plays a crucial role in male sexual response, acting at both the central and peripheral levels, and is a clear determinant of motivation to seek sexual

contact. Several studies in hypogonadal men have demonstrated that testosterone replacement has an unequivocal role in restoring sexual desire, spontaneous sexual thoughts, and attraction to erotic stimuli. The testosterone-dependency of type 5 phosphodiesterase (PDE5) expression and activity has also been demonstrated in other portions of the male genital tract (MGT), such as the VD, a critical effector for semen emission and ejaculation.

Recent data suggest that testosterone plays a facilitatory role in the control of ejaculatory reflex. Higher, with respect to controls, testosterone levels have been demonstrated in PE. Both central and peripheral mechanisms have been advocated to explain this association. The first explanation is psycho-endocrinal. Testosterone, in addition to its action on sexual response, profoundly influences general male behavior. High testosterone levels in human adults are associated with leadership, toughness, personal power, and aggressive dominance. Could this aspect be related to PE?

Another intriguing possibility involves the possible peripheral role of testosterone in regulating MGT motility. In rabbit hypogonadism, it was found that PDE5 is less expressed and biologically active in the VD. Testosterone administration completely reversed these alterations. Finally, it cannot be excluded that the testosterone differences demonstrated are the consequences of sexual disturbances mirroring differences in sexual behavior, such as copulation frequency. In conclusion, some possible mechanisms may connect androgen levels with the complex machinery of ejaculation.

The role of prolactin

In a large, consecutive series of patients interviewed using a specific, well-validated, powerful structured interview (SIEDY, a 13-item tool for the assessment of ED-related morbidities, and Middlesex Hospital Questionnaire, for the evaluation of psychological symptoms, low prolactin (PRL), levels are associated with both PE and anxiety symptoms. Interestingly, Mario Maggi and Giovanni Corona defined the condition of hypoprolactinemia, as found in EP, a new clinical syndrome in patients with sexual dysfunction. It has been demonstrated that low PRL response to a serotonergic challenge could be considered a mirror of a blunted central serotonergic function (BCSF). Basal PRL determination could be used as a marker of BCSF. In fact, the perturbation of serotonergic pathways has been considered as a possible pathogenetic mechanism involved in the development of PE and anxiety syndromes. According to Waldinger's neurobiological hypothesis, a disturbance in the central serotonin pathway (serotonin-2_C receptor hyposensitivity and/or serotonin-1_A receptor hypersensitivity) has been advocated – but never definitively demonstrated in humans – as a possible cause of LL-PE. Hypoprolactinemia seems apparently in keeping with this hypothesis. However, relatively low PRL levels were observed both in LL- and A-PE. Hence, it could be speculated that even secondary causes of PE would act mainly on influencing the brain serotonergic system.

On the other hand, this may be true also for lifelong PE: it can, in fact, be speculated that the serotonergic central changes, mirrored by low PRL levels of both types of PE, are a consequence, and not a cause, of the absence of ejaculatory control. In fact, many psychological disturbances (i.e. stress and frustration for chronic or acquired inability to enjoy sex) are able to provoke a neuroendocrine imbalance. Different abnormalities in serotonin function have been detected in patients with anxious symptoms and disorders, and the serotonin system is a primary target for drugs used in the treatment of these conditions. The classical view that anxiety is secondary to excessive serotonin activity has been challenged by more sophisticated models, which place less emphasis on global levels,

but consider different serotonergic neural circuitry and receptors, mediating different aspects of anxiety. In particular, the discovery of genetic variation in a crucial regulatory molecule within the serotonin system, the serotonin transporter, and its influence on emotional traits, provided a new foundation for understanding the neurobiological and genetic basis of emotional regulation and anxiety disorders. The final argument against the role of BCSF (which can be caused by, rather than causing PE) as a unique etiology of LL-PE is clear clinical evidence that the effectiveness of serotonergic antidepressants has been demonstrated in both LL- and A-PE.

In conclusion, low PRL seems an effect, rather than a cause of PE. In fact, many psychological disturbances (i.e. stress and frustration for chronic or acquired inability to enjoy sex) are able to provoke a neuroendocrine imbalance, such as that of the central serotoninergic system, mirrored by the relative hypoprolactinemia found in patients with PE.

The role of thyroid hormones

The impact of thyroid hyper- and hypofunction in male sexual function has been studied only recently. This is probably the consequence of:

i) the apparently low clinical significance given to male sexual symptoms in comparison with the systemic effects of thyroid hormone excess and defect;
ii) the paucity of clinical studies, as thyroid disease is less common in men; and
iii) the embarrassment of patients and physicians when discussing sexual dysfunction in the "traditional" setting of the endocrine outpatient clinic.

A high prevalence of A-PE has been found in hyperthyroid patients, whereas in hypothyroid subjects, the main sexual complaint was delayed ejaculation (DE). This finding has been consistently replied to by other independent research groups. Both ejaculatory dysfunctions reverted on achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Interestingly, suppressed levels of TSH (as a marker of hyperthyroidism) have been demonstrated in A-PE but, obviously, not in patients with LL-PE. All these data suggest a direct involvement of thyroid hormones on the physiology of ejaculation.

As the relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, 3 possible sites of action have been suggested: the sympathetic nervous system, the serotoninergic pathway, and the endocrine/paracrine system. Most manifestations of thyrotoxicosis and sympathetic nervous system activation overlap. This may suggest a similar action on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma catecholamines and their urinary metabolites are usually normal in hyperthyroidism. On the other hand, some studies have found that thyroid hormones augment sensitivity to β-adrenergic agonists by increasing β-adrenoceptor density and G_s/G_i protein ratio through an over-activation of adenylate cyclase. This leads to increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may trigger ejaculatory control, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability. Considering the neuropsychological reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, emotional lability), PE may also be a non-specific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotoninergic pathway, leading to diminished ejaculation control. In animals with experimentally-induced hypothyroid states, increased serotonin turnover in the brainstem is consistently reported

and thyroid hormone replacement is associated with increased cortical serotonin concentrations and augmentation of serotonergic neurotransmission by desensitization of the serotonin inhibitory 5-HT_{1A} (auto-inhibition). Finally, DE is a common and therapeutically useful side effect of serotoninergic drugs, indicating that this pathway is fundamental for ejaculatory control.

Another way that thyroid hormones may affect the ejaculatory mechanism could be through estrogen metabolism. Hyperthyroidism increases levels of sex hormone binding globulin (SHBG), which binds androgens with higher affinity than oestrogens, leading to a relative hyperestrinism. It has been demonstrated in hypogonadic rabbits that estrogens, but not androgens, fully restore OT-induced epididymal contractility, up-regulating OT receptor gene and protein expression, and that deprivation of endogenous estrogens induces OT hypo-responsiveness. It has been emphasized that many men with LL-PE report having rapidly occurring erections (*erectio praecox*). Because OT strongly facilitates erection, *erectio praecox* in the context of LL-PE may be associated with increased OT release during coitus. Whether there is a premature burst of OT released from the neurohypophysis into the systemic circulation in patients with LL-PE is not yet known. As OT is closely involved in the ejaculatory mechanism, both centrally and peripherally, this may account for the close correlation between hyperthyroidism and PE. As an ancillary possibility, thyroid hormone receptors have been described in the animal and human testis, and may also be present in other MGT structures, leading to ejaculation. Finally, some cases of PE in hyperthyroidism are comorbid with impotence, which may in turn exacerbate the loss of ejaculatory control.

Finally, hyperthyroidism in experimental animals leads to enhanced SV contraction frequency and bulbospongiosus muscle contractile activity. In rats, T_3 administration affects the emission and expulsion phases of ejaculation in reversible fashion. The changes probably take place in the supraspinal centers above T_8 level. This interesting animal evidence suggests that, in keeping with the pleiotropic role of thyroid hormones, T_3 may act at multiple levels in controlling ejaculation.

Endocrinology of DE: towards a unifying theory

DE can be simply defined as "slowness to ejaculate" (as reported by the patient), or, accordingly to the current edition of the reference manual of psychiatry (DSM IV-R) as:

> a persistent or recurrent delay in, or absence of orgasm in a male following a normal sexual excitement phase during sexual activity, that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration.

This definition is not rooted on any IELT evidence. In particular, severity of DE is categorized on a 5-point scale using the standard question: "In the last three months, has it been difficult to ejaculate during sexual intercourse?" and rating:

0 (no DE):
1 (mild DE), if ejaculation and climax were still possible, but only with great effort and after prolonged intercourse;
2 (moderate DE), if ejaculation and climax were still possible only with autoerotism, although in the presence of a partner, but not during coitus;
3 (severe DE), if orgasm and ejaculation could be obtained only with autoerotism conducted in the absence of a partner; and
4 (anejaculation), if orgasm and ejaculation could not be obtained at all.

Marcel Waldinger, first stated that LL-DE, like LL-PE, can be considered a neurobiological variant, which may or may not secondarily

lead to psychological or psychosocial distress. So far, we do not have direct evidences of this interesting theory. However, hormonal levels found in DE, when compared with PE, may allow us to build a unifying theory, a sort of continuum having the extreme DE, which is anejaculation, on one side, and extreme PE (*ejaculatio ante portas*, i.e. before penetration) on the other.

When comparing DE and PE, PRL as well as TSH levels progressively increased from patients with severe PE toward those with anejaculation. Conversely, the opposite was observed for testosterone levels. All of these associations were confirmed after adjustment for age. When these hormoneal parameters are introduced in the same regression model, adjusting for age, general psychopathology, and use of selective SSRIs, they are independently associated with ejaculatory problems. This indicates that the endocrine system is involved in the control of ejaculatory function and that PRL, TSH (as a marker of thyroid activity), and testosterone play an independent role.

Basal, non-stimulated PRL, in the normal physiological range, could mirror the central serotoninergic tone. This could be related to the significantly higher PRL levels found in DE, when compared with anejaculation or PE.

While hyperthyroidism is characteristic of PE, hypofunction of the thyroid is clearly associated with DE. It seems likely that while excessive presence of thyroid hormones may decrease the ability to control ejaculation, the low levels of T3 may increase the ejaculatory threshold.

Hypogonadism has been found to be significantly associated with DE. The latter symptom has been considered to be essentially characterized by the uncoupling of a decreased subjective and a preserved genital reaction in sexual arousal. It could thus be speculated that hypogonadism and related reduction in sexual confidence and aggressiveness could play a critical role in the control of ejaculation timing, reducing the internal cues for reaching orgasm and ejaculation. The second hypothesis is neurological. Recent data from animal models seem to support the central action of testosterone in the control of the ejaculation reflex. It has been demonstrated that long-term testosterone treatment in rats significantly decreased 5-HT in the brain. Furthermore, testosterone can be aromatized by cytochrome P450 aromatase to an active estrogen, 17β-estradiol (the enzyme aromatase is widely expressed in MGT, in particular, in the epididymis). In the epididymis, testosterone, but more efficiently its metabolite estadiol, can revert hypogonadism-induced down-regulation of the RhoA/ROCK pathway (a calcium-sensitizing pathway) and restore contractility. A "mechanical" mechanism of testosterone action in ejaculation control can also be possible. A hypogonadism-induced reduction in semen volume may perturb the dynamics of the seminal bolus propulsion, possibly explaining ejaculation difficulties in some subjects. In fact, low testosterone directly reduces ejaculate volume, which may result in a lack of stimulation of accessory glands such as the prostate and SV, which are well-known androgen targets. Hence, low testosterone should be suspected and analyzed in all subjects with DE (Figure 7.1).

In conclusion, from a psycho-neuroendocrine perspective, PE and DE can be considered 2 ends of a single continuum, spanning from severe PE to extreme DE (Figure 7.2). In addition, although endocrine regulation of the ejaculatory reflex is still in its infancy, evidence so far produced indicates that it should grow rapidly to help shed light on often-occurring but seldom-studied conditions, such as ejaculatory disturbances.

Endocrine related therapies of ejaculatory disturbances

Endocrine therapies are widely available and very effective in treating the cognate underlying conditions. It is possible that endocrine therapy of ejaculatory disorders, whenever indicated, ameliorates not only sexual life but

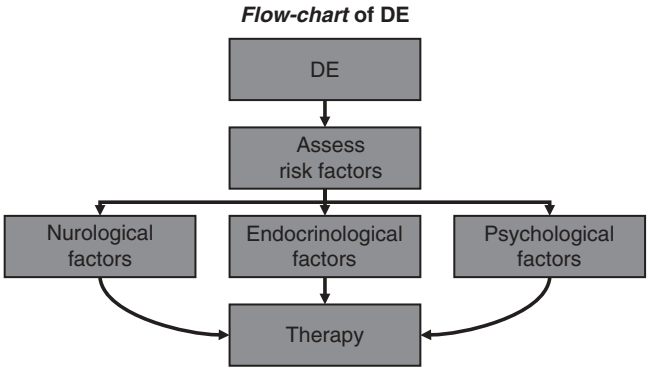


Figure 7.1. Flow-chart of delayed ejaculation.

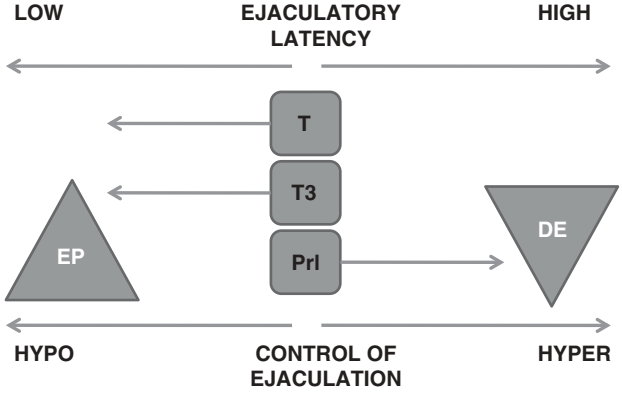


Figure 7.2. The hormonal regulation of the ejaculatory *continuum*.

also the overall health of our patients, as could be the case for thyroid or testis disorders.

Opiatergic therapy

Tramadol is an analgesic drug binding, with its metabolites, as morphine, the μ-receptor. Furthermore, it inhibits 5-HT and noradrenaline re-uptake. A couple of placebo-controlled studies suggest that tramadol might be effective for the on-demand treatment of PE. However, these findings are preliminary and, as with all opioids, there might be concerns about the risk of abuse/dependence.

OT receptor antagonists

The idea to target OT receptors for PE comes from different observations:

i) the intensity of muscular contractions during orgasm in men correlated with OT plasma level;
ii) stimulation of the dorsal penile nerve and tactile stimulation of the glans penis provoke a specific activation of oxytocinergic neurons in the paraventricular nucleus of the hypothalamus, leading to the release of OT at ejaculation;
iii) 5HT also suppresses ejaculation by interrupting the action of OT; in fact, OT administration reversed the effect of fluoxetine on ejaculation. The effects of OT administration could have been mediated by a central stimulation of sympathetic outflow or peripherally by facilitating smooth muscle contraction in the reproductive tract; and
iv) more OT neurons are activated in rapid ejaculatory rats compared with "sluggish" and "normal" ejaculators.

Several findings on experimental animals are in keeping with these possibilities.

Several OT receptor inhibitors (i.e. the tocolytic drugs) are under development for the treatment of several disorders, including preterm delivery, obesity, and PE. Whether OT receptor antagonists could be a potential addition to the therapeutic armamentarium for PE are awaiting further investigation to address the arguments against the use of OT receptors antagonists in PE.

Treatment with androgens

So far, no clinical trials have been produced showing how effective could be testosterone replacement in hypogonadal patients with DE. However, it seems very likely that well-designed studies will show this effect in the near future.

Prolactin

The levels of PRL in patients with PE and DE, although correlated with these 2 symptoms, are always within the normal range. Hence, a modulation of prolactin production in the ejaculatory disturbances is not advisable.

Treatment of thyroid hormone-induced ejaculatory disturbances

Consistent evidence shows that full recovery from ejaculatory hyper- and hypo-control can be obtained in several patients, restoring euthyroism. It is mandatory to treat hyperthyroidism, even in its sub-clinical form, because this disease, having PE in the cohort of symptoms, is associated with a dramatic increase in all-cause mortality, especially in men. The medical treatment of the opposite state, hypothyroidism, results in a 2-fold decrease in ejaculatory latency and a reduction in DE. If not treated, hypothyrodism, provoking several mood, metabolic, and systemic symptoms, can jeopardize both quality of life and survival. Thus, the need to recognize this condition in patients with DE seems evident.

In the real-life clinical experience, not all patients successfully treated for prostatitis (an important risk factor of PE) or hyperthyroidism achieve good ejaculatory control. Many of them develop a secondary psychological concern regarding their ability to delay ejaculation, which needs counselling and, frequently, pharmacological treatment with SSRI. However, it is also well known that A-PE due to psychosocial aetiologies is often refractory to psycho-sexological approaches, such as behavioral therapies. Future research may demonstrate that the first PE-tailored drug dapoxetine increases the efficacy of psychological treatments, being effective not only in LL-PE but also in A-PE. This treatment may also be considered in patients not reaching the perfect ejaculatory control when completely euthyroid.

In any case, being both hyper- and hypothyroidism-associated PE easily treatable conditions, clinical screening with eventual laboratory confirmation for thyroid diseases in men with ejaculatory dysfunction is strongly advised.

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8

Paraphilic Disorders: Diagnosis and Treatment

Alessandra D Fisher, Elisa Bandini, Helen Casale, and Mario Maggi

University of Florence, Florence, Italy

Definition, diagnosis, and comorbidities

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR), paraphilias are defined as sexual disorders characterized by recurrent, intense, sexually arousing fantasies, urges, or behaviors, over a period ≥6 months, generally involving:

(1) non-human objects;
(2) suffering or humiliation of oneself or one's partner;
(3) children or other non-consenting persons (criterion A).

These fantasies, urges, and behaviors produce clinically significant distress or impairments in social, occupational, and other important areas of functioning (criterion B).

For pedophilia, voyeurism, exhibitionism, and frotteurism, the diagnosis can be made also in the absence of personal distress, if the individual acts on the sexual urges. With the other paraphilias (not involving other persons), the diagnosis can be made only if the sexual urges and/or fantasies produce the effects listed in criterion B (see below).

SCIENCE REVISITED

Paraphilia definitions (DSM-IV-TR; 302)

Criterion A

Recurrent, intense, sexually arousing fantasies, urges, or behaviors, which occur over a period of ≥6 months, generally involving:

- non-human objects;
- suffering or humiliation of oneself or one's partner; or
- children or other non-consenting persons.

Criterion B

- which cause clinically significant distress or impairments in social, occupational, and other important areas of functioning.

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Table 8.1. Different kinds of paraphilias, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edn, Text Revision (DSM-IV-TR) classification. Identification code numbers from DSM-IV-TR in parentheses

Exhibitionism (302.4)	Exposure of genitals to unsuspecting strangers (is NOT the same as public urination)
Fetishism (302.81)	Use of non-living objects as a repeatedly preferred or exclusive method of achieving sexual excitement (e.g. leather goods, clothing, undergarments, fabrics, shoes). (If female clothing is used in cross-dressing or devices are used to directly stimulate the genitals – e.g. vibrator – this is NOT a fetishism).
Frotteurism (302.89)	Touching and rubbing against a non-consenting person
Pedophilia (302.2)	Children are the sexual target (perpetrator is ≥16 years old and ≥5 years older than the victim).
Sexual masochism (302.83)	Perpetrator receives the humiliation/suffering (practice can even lead to death, especially during "hypoxyphilia" or sexual arousal during hypoxia).
Sexual sadism (302.84)	Perpetrator inflicts the humiliation/suffering on another (generally, severity increases over time).
Transvestic fetishism (302.3)	Wearing clothing of the other sex for sexual arousal.
Voyeurism (302.82)	Observing sexual activity or naked/disrobing individuals.
Paraphilias Not Otherwise Specified (302.9)	This category is included for coding Paraphilias that do not meet the criteria for any of the specific categories. Examples include, but are not limited to, telephone scatologia (obscene phone calls), necrophilia (corpses), partialism (exclusive focus on part of body), zoophilia (animals), coprophilia (feces), klismaphilia (enemas), and urophilia (urine).

DSM-IV-TR describes 8 specific disorders of this type, along with a residual category called "paraphilias not otherwise specified" (Table 8.1).

In total, more than 50 types of paraphilias have been described, most of them being more common in men (~90% in Europe) than in women, except for sexual masochism.

The average age expression of the disorder is paraphilia-specific. Paraphilias may begin in childhood or early adolescence, but paraphilic sexual interest frequently becomes more defined during adolescence. The mean ages of onset of paraphilias are: transvestic fetishism, 13.6 years; fetishism, 16.0 years; voyeurism, 17.4 years; non-incestuous homosexual pedophilia, 18.2 years; exhibitionism, before 18 years; sadism, 19.4 years; and non-incestuous heterosexual pedophilia, 21.1 years. Therefore, the onset of most paraphilic disorders is around the time of puberty, running a chronic course. The frequency of sexual acts may increase or decrease over time, but often diminishes with advanced age (≥60 years old).

Stimuli can be either obligatory for erotic arousal and always a component of the sexual activity ("exclusive paraphilia"), or can be episodic (e.g. only if the individual is stressed) and the individual may be aroused by other fantasies, stimuli, and behaviors, although their paraphilias may interfere with their overall sexual preference ("non-exclusive paraphilia").

Paraphiliacs often have more than one type of deviant sexual behavior and 50–70% of pedophiles seem to have more than 1 paraphilia.

Paraphilias can be graded from mild to catastrophic, depending on the history of victimization and, if present, the number of victims, their age, and the degree of victimization (level of intrusiveness: penetrative or not) are considered. Severe cases would involve more than 1 victim or a child, and there would be penetration to some degree. In general, individuals with exhibitionism or pedophilia make up the majority of apprehended sex offenders. The mean number of victims for one pedophile is around 20.

It is important to remember that not all sex offenders suffer from paraphilias, but only a part of them and, vice versa, that not all patients with paraphilias are sex offenders. In fact, paraphilic subjects, in many cases, only suffer from deviant sexual fantasies or urges, or their deviant sexual behavior does not involve a non-consenting person or a child. These subjects may present for treatment because of the associated distress of their personal lives. In contrast, other paraphilic behaviors may lead to sex offenses, a major public health problem defined as any violation of established legal or moral codes of sexual behavior. For example, clinically defined sexual behaviors such a pedophilia, voyeurism, frotteurism, and exhibitionism are also considered sexual offenses but, for instance, fetishism and transvestic fetishism are not. On the other hand, crimes such as rape are not classified as paraphilias. Simply having a paraphilia is obviously not illegal. However, acting in response to paraphilic urges may be illegal and, in some cases, subjects the person with paraphilia to severe sanctions.

CAUTION

While some paraphilias can be associated with strange sexual behaviors, they are not necessarily associated with offenses.

Many studies have consistently found high prevalence rates of comorbid psychiatric disorders in patients with paraphilia. Associated psychiatric disorders include major Axis I mental illness, as affective disorders, substance abuse disorders, schizophrenia, other psychotic disorders, and dementia (especially temporal and/or fronto-temporal dementias). Moreover, paraphilias can occur within the context of personality disorders, such as borderline or antisocial personality disorders, within mental retardation, and other medical conditions, such as temporal lobe epilepsy or brain trauma, Huntington disease, and Kluver Bucy and Kleine Levin syndromes. Finally, paraphilias may also occur in patients undergoing dopamine receptor agonist therapy, for example for Parkinson's disease. Paraphilias often result in a variety of psychological disturbances, such as guilt, depression, shame, isolation, and impaired capacity for normal social and sexual relationships.

The differential diagnosis includes developmental disability, dementia, personality changes due to general medical conditions, substance intoxication, manic episodes, and schizophrenia.

Prevalence of paraphilias

Actual prevalence/incidence figures are unavailable for all of the paraphilias. According to a few studies, paraphilic sexual fantasy seems to be common in the general population.

The prevalence of paraphilias is mainly derived from the prevalence of sex offenses. However, the latter number is often underestimated, either because offenders have never been apprehended or the offense did not result in conviction. Moreover, many sexual assaults are unreported or undisclosed by the victim, due to feelings of shame or guilt.

Surveys have provided some useful data regarding the epidemiology of pedophilia. In one US survey of 4,000 females, 24% stated

that they had experienced sexual interaction with a male ≥5 years older than themselves when they were ≤14 years old. Intercourse occurred in only 3% of cases, with minor petting or fondling without genital involvement in 31% of cases. In a Canadian National Population Survey of 2008 subjects (1,005 females, 1,003 males) 18.1% (23.5 and 12.8% of females and males, respectively) reported that they had been victims of sexual violence when they were children or adolescents.

Recidivism is a major concern in the treatment of paraphilia, especially in pedophilia. Published recidivism rates among pedophiles range from 10–50%, depending on how subjects are grouped. Non-related pedophiles exhibit higher rates, while incestuous pedophiles have the lowest rates. Homosexual and bisexual pedophiles have higher rates than heterosexual pedophiles (50 and 25%, respectively). Moreover, higher rates of recidivism seem to be also associated with more deviant sexual practices, addictive disorders (mostly alcoholism or drug abuse), psychiatric comorbid disorders, attraction to younger children, display of more sociopathic or antisocial personality traits, higher rates of treatment non-adherence, and a greater number of paraphilic interests reported by the offender. It is important to remark that no test or instrument capable of predicting the future activity of a pedophilic individual exists.

Etiology

Although the etiology of the paraphilias is unknown, the neurophysiology of sexual arousal has been the subject of much research and has led to the pharmacologic approaches used today. Sexual arousal is dependent on neural (sensory and cognitive), hormonal, and genetic factors, and in humans, the complex influences of culture and context.

Many physiological substances produce stimulating or inhibiting effects on different sexual processes in the central nervous system, the peripheral nerves, and the genital organs. α1-Adrenergic and dopaminergic neurotransmission enhances sexual arousal, as does parasympathetic muscarinic neurotransmission. Serotonergic neurotransmission reduces sexual arousal. Norepinephrine (via alfal-adrenoceptor activation) and acetylcholine (via muscarinic receptor activation) stimulate sexual arousal. Numerous neuropeptides enhance sexual arousal (enkephalins, oxytocin, gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)), either by themselves or by enhancing production of other compounds. Hormones that affect sexual arousal include prolactin (reduces it), testosterone (T)/dihydrotestosterone (DHT, increases it), and estrogen/progesterone (increases it).

In particular, T plays a well-known crucial role in male sexuality. Some evidence in animal models shows that T modulates serotonin receptor effects on impulsive aggression. The role of this hormone in human aggression is less clear. Male prisoners with a history of violent crime during adolescence or chronic violent behavior seem to have higher T levels than prisoners convicted for non-violent crimes. Moreover, a study has reported that high free T levels in the cerebrospinal fluid discerned violent from non-violent alcoholic offenders. However, most studies focused on this topic are characterized by inconsistency.

Furthermore, many authors have suggested a close relationship between paraphilias and the obsessive-compulsive disorders, hypothesizing a dysregulated serotonin system.

Ethical issues

The treatment of patients with paraphilias, irrespective of which method of treatment is employed, has always been surrounded by clinical and ethical dilemmas.

The major ethical issues regarding sexual offenders, including paraphilias, may reflect the dispute between the need for public safety and on the other hand, the consent of the

patient to be treated. Moreover, such kinds of crimes make the public and even professional opinion lean toward punishment rather than treatment, even when appropriate and effective. For example, imprisonment may stop pedophiles from committing illegal sex acts against children, but it does not change the pedophile's internal sexual orientation. Treating pedophilia is critical in an approach to preventing sexual violence and reducing victimization. In addition, it provides a more humane and lasting solution than imprisonment and may at least be used concomitantly.

Paraphilic sex offenders may be ordered by a judge to undergo treatment as part of a rehabilitative aspect of sentencing. Moreover, this decision should be made by a psychiatrist with the required qualifications, after examination of the person concerned and after an informed consent has been obtained. However, doubts about the validity of consent have risen, because consent is sometimes given in situations where the person is subject to some external pressure. In cases of doubt with regard to the validity of the patient's consent, after withdrawal of his consent or non-compliance with the treatment, the decision to subject a sex offender to coerced treatment should be made by a court or another competent body.

The court or other competent body should:

- act in accordance with procedures provided by the law, based on the principle that the person concerned should be seen and consulted;
- not specify the content of the treatment, but force the sex offender to comply with the treatment plan negotiated with the psychiatrist.

From an ethical point of view, if the paraphilic sex offenders need hormonal therapy, this should be allowed only if all of the following conditions are met (Belgian Advisory Committee on Bioethics 2006 www.health.fgov.be/bioeth; Council of Europe 2004):

- the person has a paraphilic disorder diagnosed by a psychiatrist after a careful psychiatric examination;
- the hormonal treatment addresses specific clinical signs, symptoms, and behaviors and is adapted to the person's state of health. It must be part of a more detailed treatment program which, in addition to the psychiatric part, also considers the psychological and social aspects. The hormonal treatment cannot be the only measure imposed on sex offenders on the basis of the nature of the crimes committed;
- the person's condition represents a significant risk of serious harm to his health or to the physical or moral integrity of other persons;
- when hormonal castration is considered, the advice of an endocrinologist is required first;
- hormonal treatment is a medical treatment for which the psychiatrist in charge of the patient takes responsibility:
 - for the indication;
 - to inform the person involved and to receive his consent
 - for the follow-up, including somatic aspects with the help of a consultant endocrinologist, if necessary;
- the therapist will always give preference to the least intrusive intervention to obtain a particular result. If a less intrusive alternative treatment exists instead of hormonal treatment, this alternative must be preferred;
- the hormonal treatment is part of a written treatment plan to be reviewed at appropriate intervals and, if necessary, revised.

☆ TIPS & TRICKS

How to evaluate a sex offender/paraphilic subject:

- demographic characteristics of the subject;
- age, gender, marital status, children (number, gender, and age), educational level, employment status (with or without children);

- family and personal history of psychiatric disorders and sexual disorders or related treatment, suicide attempts, history of sexual abuse or use of violence.

Characteristics of paraphilia:

- conventional and paraphilic sex fantasies and activities, exclusive or not exclusive paraphilic behavior, age at onset of paraphilic behavior, type and number of paraphilia, gender and age of victims, intra-familial or not, internet or video use, violence, alcohol or illicit drug consumption before paraphilic behavior;
- interpersonal relationships, insight, empathy, coping with stress, impulsivity, motivation for treatment;
- comorbidity with Axis 1 or Axis 2 of the DSM classification, comorbidity with somatic diseases, cognitive evaluation (dementia, mental retardation).

Therapeutic approaches

The heterogeneous characteristics of paraphilias demand that treatment options are integrative and include a number of different approaches. Treatment modalities currently used for paraphilic behaviors fall basically into 3 categories:

1) Psychotherapy
2) Pharmacotherapy
3) Androgen deprivation (surgical/chemical castration)

The aim of psychotherapeutic interventions is, in general, to change the sexual behavior of the offender leaving libido intact; pharmacological interventions seek to greatly diminish or altogether eradicate sexual desire and capacity.

The treatment choice will essentially depend on:

- the patient's previous medical history;
- the patient's compliance;
- the intensity of the paraphilic sexual fantasies;
- the risk of sexual offense.

The aims of the treatment for paraphilias are:

- to control paraphilic fantasies and behavior in order to decrease the risk of recidivism;
- to control sexual urges;
- to decrease the level of distress of the paraphilic subject.

Therefore, the effectiveness of any therapy is usually determined by the degree of reduction in intensity of the abnormal sexual fantasies, desire, and behavior. However, the decrease or abolishment of the recidivism of the abnormal sexual behavior is considered to be the single most important index of therapeutic success.

Limitations in assessing treatment efficacy

In general, treatment efficacy studies are marked by some methodological bias and are extremely difficult for several reasons: small sample sizes leading to false negative results and difficulties in conducting studies with forensic patients; sex offending is not socially acceptable and those who suffer from it rarely seek treatment voluntarily. Most reports on the treatments of paraphilias are case reports or series. Moreover, due to ethical reasons (high risk of recidivism, low level of motivation of the patient, denial, prisoners in most cases, etc.), the great majority of pharmacological studies are uncontrolled studies without placebo comparison. In addition, inasmuch as sexual offenses are typically under-reported, recidivism rates identified from official criminological records also represent an under-representation of the "true" recidivism rate. Very large samples,

including a matched control group, and long follow-up periods, would be necessary to identify a truly statistically significant effect of treatment on outcome.

Psychotherapy

Psychotherapy can be divided into individual and group or family therapy. Most commonly, it is a combination of both approaches. The psychoanalytic treatment for paraphilic patients is more valued for its meaningful approach in understanding than for its outcome evidence. Cognitive behavioral therapy is today the most frequently used therapy and cognitive behavioral principles are the basis of the prison-based sex offender treatment programs. This approach is aimed at changing internal processes, along with changing overt behavior, such as social skills or coping behaviors. This type of therapy has been considered the "gold standard" non-pharmacologic approach offered to pedophiles. Treatment could be focused on altering deviant sexual arousal patterns, addressing social skill deficits that may contribute to sexually delinquent behavior, challenging beliefs that can facilitate sex offending behavior, and developing strategies to prevent a re-occurrence of sexual offenses. Behavioral techniques, which decrease sexual deviancy, involve olfactory aversion conditioning (using an unpleasant smell, such as ammonia), covert sensitization (imagine deviant sexual experience until arousal and then imagine a powerful negative experience), aversion therapy (exposure to deviant material followed by aversive stimulus), and masturbatory satiation to decrease deviant sexual arousal and cultivate appropriate sexual response patterns. Moreover, treatments are designed to improve a sex offender's social competence, interpersonal and functional social skills, and self-esteem. The psychosocial treatment dimension has broadened to include training in anger management, relaxation, and interventions to promote empathy with the victim and awareness.

Irrational beliefs, such as beliefs that sex with children is a way to teach them about sexuality or that most women enjoy being raped, can contribute to an individual's justifying and engaging in deviant and criminal sexual behavior. Treatment to alter distorted beliefs entails the identification of and challenges to these kinds of cognitive distortions through cognitive restructuring techniques. However, these kinds of approaches are costly, and the effects in clinical trials have been extremely variable (including helpful, not helpful, and/or harmful, even in the same trial). This extreme variability may be related, in part, to the need for the offender to admit guilt and accept personal responsibility before success is possible, and to the media who bias the public to believe in the universal failure of these treatments. The cognitive behavioral therapy for sex offenders brings a modest reduction in recidivism, but this is not supported by studies with longer follow-up periods. The other approaches (psychosocial programs, therapeutic communities, insight-oriented treatment) do not seem to reduce recidivism.

In summary, to date there is much debate concerning the overall effectiveness of psychotherapy approaches for the long-term prevention or Androgen deprivation therapy of new offenses and several studies have reported that the best outcomes in preventing repeat offenses against children occur when pharmacological agents and psychotherapy are used together.

Pharmacologic Therapies

Pharmacological treatments are used in order to decrease the general level of sexual arousal.

The use of psychotropic medications in paraphilic behavior is not new, but there are no randomized controlled trials that have documented their efficacy. Unfortunately, the level of evidence is very poor.

Lithium carbonate, tricyclic antidepressants (clomipramine, desimipramine), mirtazapine, antipsychotics (benperidol,

thioridazine, haloperidol, risperidone), and anticonvulsants (carbamasepine, topiramate, divalproate) have been sporadically used over the years.

Selective serotonin reuptake inhibitors (SSRIs)

Research evidence on the efficacy of antidepressants for treatment of paraphilic sexual offenders has been reported. The World Federation of the Society of Biological Psychiatry recommends the use of SSRIs in the treatment of sexual abusers in the case of:

- *juvenile paraphilias*: paraphilias usually start at adolescence and are limited to deviant fantasies related to masturbation between 12 and 18 years. SSRIs given at this stage could prevent acting out of deviant behaviors;
- *mild paraphilias*;
- *comorbidity with obsessive-compulsive disorder, impulse control disorder or depression*: some paraphiliacs clearly suffer from an inability to resist their sexual urges, which have a strong compulsive element and often cause a considerable subjective distress in maintenance treatment.

The rationale for the use of SSRIs in sexual offenders is based on the following evidence:

- it is well known that increased levels of serotonin (5HT) in the hypothalamus inhibit sexual motivation and the T signaling, while increased levels of serotonin in the prefrontal cortex enhance emotional resilience and impulse control. In pedophilia, decreased activity of the 5HT presynaptic neurons and up-regulation of postsynaptic 5HT-2A receptors has been reported.
- SSRIs have been shown to decrease impulsion in antisocial impulsion, anxiety, depression, and hypersexuality.
- Important Axis 1 and Axis 2 comorbidities have been reported in juvenile and adult paraphilics and hypersexual subjects. It is recommended that this disorder be treated as well.

On these bases, several guidelines have been developed for the treatment of sexual offenders, which are summarized regarding the indication of SSRIs:

- The Association for the Treatment of Sexual Abusers included SSRIs as one of the interventions for the control of sexual arousal, within a comprehensive treatment program. These guidelines recommend SSRIs for patients with high levels of arousal that cannot be controlled with cognitive behavioral therapies, adding that informed and motivated patients are good candidates.
- The American Academy of Child and Adolescent Psychiatry recommends cognitive behavioral interventions, psychosocial interventions, and SSRIs for children and juveniles who are sexual abusers. The use of antiandrogens is discouraged under 17 years of age, as they could delay the onset of puberty and bone growth.

Androgen deprivation (surgical or hormonal castration)

Androgens play a crucial role in sexual interest and associated sexual arousal, which is defined as a state that motivates the individual toward the experience of sexual pleasure and possibly orgasm. Consequently, a reduction in circulating T may be helpful in decreasing sexual interest, arousal, fantasies, and behaviors, resulting in either a marked reduction or abolishment of the paraphilic manifestations. This principle has been put into practice in the androgen deprivation therapy for sex offenders. Moreover, it has been reported that serum T levels predicts sexual recidivism and higher T levels have been found to be associated with more invasive sexual crimes in sexual offenders. In fact, the benefit of androgen deprivation therapy is in diminishing the intensity of the eroticized urges that energize

unacceptable paraphilic behaviors and it can, in turn, facilitate the resisting of those urges.

On the other hand, normal levels of androgens play a crucial role in male bone health and are required for a large number of metabolic aspects, mood, erythropoiesis, sebaceous gland activities, and several other functions. Therefore, severe androgen deprivation is associated with several pathological effects on these biological systems. In particular, androgen deprivation therapy with surgical castration, antiandrogens, or analogs of gonadotropin-releasing hormone (GnRH analogs) induces in men a rapid bone loss, typically in the spine, hip, and forearm, but also at appendicular skeletal sites such as the femoral neck. Bone mineral density decreases within 1 year after the start of these therapies, with a continuing decrease causing bone loss thereafter (~3–7% per year in lumbar spine). The consequent increased risk of osteoporotic fracture is increased even further by changes in body composition induced by hormonal castration, such as increases in weight and body mass index and decreases in lean body mass and muscle mass/strength. It is therefore recommended that bone mineral density be measured by dual energy X-ray absorptiometry (DEXA) before the therapies start, in particular in subjects at high risk, to detect pre-existing osteoporosis and to monitor significant bone loss over time. Effective prophylactic and therapeutic strategies for this musculoskeletal effect are being investigated; they include calcium (1,200–1,500 mg/day) and vitamin D supplementation (400–800 IU daily). Patients should be advised to abstain from smoking and excessive alcohol use. Moreover, bisphosphonates (e.g. oral alendronate or risedronate, and parenteral pamidronate or zoledronic) have been successfully used in reducing bone loss in patients receiving antiandrogens. The use of this class of drug is recommended in men with ostedensitometry-proven osteoporosis or in men with osteopenia and pre-existing bone insufficiency fractures (due to minimal trauma). Furthermore, parathyroid hormone (or a congener such as teriparatide) therapy, and selective estrogen receptor modulators, such as raloxifene, are also being investigated. Finally, a low-dose androgen supplementation (e.g. testosterone enanthate 25–50 mg/month) has been considered. This latter, moreover, may also ameliorate the erectile failure and thus improve appropriate sexual relationships with partners, whereas all paraphilic manifestations remain totally suppressed.

Moreover, men treated with androgen deprivation therapy develop an increase in body and fat mass, hyperinsulinemia, hyperglycemia, insulin resistance, and impaired lipid profile, with an increased risk of developing metabolic syndrome, diabetes mellitus (by 40–50%), and cardiovascular diseases (by 10–20%). To reduce these side effects, it is important that patients adopt a healthy lifestyle and dietary behaviors, including smoking cessation and regular exercise. Such non-pharmacological interventions can be followed by statin therapy, in order to lower the blood low-density lipoprotein levels and reduce the risk of cardiovascular events. Proposed target levels, derived from research in type 2 diabetes, are as follows: low-density lipoprotein cholesterol levels, <2.6 mmol/l (100 mg/dl); fasting triglycerides levels, <1.7 mmol/l (150 mg/dl); and high-density lipoprotein cholesterol levels, >1.1 mmol/l (40 mg/dl).

Concerning mood disturbances, low T levels have been associated with an increased risk of depression, emotional disturbances, anxiety, fatigue, malaise, memory difficulties, asthenia, lack of drive, and listlessness. It should further be taken into account that paraphilic individuals suffer frequently from comorbid affective disorders or other mental illnesses, with an increased risk of bipolar depression after the start of hormonal therapy. Moreover, conviction, imprisonment, and the stigma and shame of being a sexual offender may

also increase the risk of depression. Sex offenders should therefore be carefully evaluated before the start of and during androgen deprivation therapy, for the presence of mental illnesses, to provide appropriate psychiatric treatment.

Other side effects of androgen deprivation include hot flushes and night sweats, which may reduce quality of life. Hot flushes can be effectively treated with megestrol acetate and SSRIs and selective serotonin-norepinephrine re-uptake inhibitors (SRNIs), which also may be beneficial in treating comorbid depressive symptoms. Moreover, other side effects that have been described are breast tenderness and gynecomastia, especially using cyproterone acetate. Radiation, at a single dose of 1,500 cGy per breast, has been used to prevent or treat painful/tender gynecomastia caused by this drug. After 3 and 6 years of follow-up, the further development of gynecomastia was halted, and pain and tenderness were reduced to minimal. Furthermore, besides impotence and its libido-reducing effects, androgen deprivation therapy also directly induces partial azospermia and infertility, although it provides no birth control assurance.

For all these reasons, effective and wise management of sex offenders treated with T deprivation therapy should include careful monitoring of side effects and their prevention. Sex offenders who start a treatment should furthermore be aware that this intervention is not without risk.

Androgen deprivation treatment should be used after other alternatives have been ruled out or when there is a high risk of sexual violence. Not every sex offender is a candidate for hormonal treatment, even if it has the advantage of being reversible once discontinued. Moreover, it cannot be frequently used in the treatment of juvenile sex offenders, because of the possible interference with the development or course of puberty (bone growth must be achieved and should be checked using X-rays).

Surgical castration

Orchidectomy reportedly produces definitive results, even in recidivist pedophilic offenders, by reducing thus from 5 to 2%. However, up to one-third of castrated males can still engage in intercourse. Therefore, it is not uniformly effective in producing impotence. Results can also be reversed by the administration of exogenous T, allowing re-offense. From the introduction of surgical castration in Switzerland in 1892 (as a treatment for hypersexuality) until the 1970s, this procedure has been used in many European countries and in the United States. Today, it is available only in Germany and in certain US states. One significant factor, considering limited prison health care budgets, is the substantial difference in cost between one-time surgical castration and ongoing chemical castration with anti-androgen drug therapy.

On the other hand, since medication is available that produces similar results, the Belgian Advisory Committee on Bioethics have recently advised that surgical castration can no longer be an option for the treatment of sex offenders.

Hormonal castration

Estrogens

Estrogen therapy has a long history of use in sex offenders. The first use of oral diethylstilbestrol (DES) was reported in 1940, followed in that decade and subsequent ones by the use of oral estronen. Estrogen therapy in males is associated with risk. Although breast cancer in males is extremely rare (lifetime risk of 1 in 1,000), there are case reports of breast cancer in men receiving estrogens. The major concerns with oral estrogen therapy in men are cardiovascular toxicity, including ischemic heart disease (myocardial infarction, angina, and heart failure), cerebrovascular disease (stroke and transient ischemic attacks), edema, and thromboembolism (deep venous thrombosis and pulmonary embolism). Although the initial negative data were associated with

high-dose DES therapy (5 mg/day), numerous trials using DES doses of 1–3 mg/day had cardiovascular adverse-event rates ranging from 10–35%. Concurrent administration of warfarin (1 mg/day) does not appear to lower these rates. Similar adverse-event potential exists with conjugated estrogen and estradiol.

In conclusion, estrogens must not be used in sex offenders or subjects with paraphilia.

Antiandrogens

Steroidal antiandrogens, such as Cyproterone Acetate and Medroxyprogesterone Acetate, have progestogenic activities in addition to their antiandrogenic effects which, through feedback effects on the hypothalamo-pituitary axis, inhibit the secretion of LH, resulting in a decrease in circulating levels of both T and DHT. These compounds interfere with the binding of DHT (the androgen that plays the dominant role in androgenic response) to androgen receptors and they have been shown to block the cellular uptake of androgens.

Cyproterone Acetate (CPA)

CPA is a synthetic steroid, similar to progesterone, which acts as a potent, dose-dependent antiandrogenic and progestational agent. Three potential mechanisms underlay its antiandrogenic effects. It inhibits the intracellular uptake of androgens, blocking their binding to the receptor through competitive inhibitions. It also blocks T (and estrogen) synthesis in the gonads. Finally, due to its powerful progestational activity, it causes inhibition of gonadotropin secretion, and blocks their compensatory rise expected to follow a decrease in serum T concentrations. This latter effect is in contrast with that of the pure antiandrogens (e.g. flutamide). When the latter agents compete with T for binding to androgen receptors, a compensatory rise in gonadotropin secretion occurs; this increase, in turn, stimulates T production and eventually overcomes the receptor blockade. The antiandrogenic effect of cyproterone acetate is believed to outweigh the progestational effect in terms of clinical efficacy in the treatment of paraphilias; however, it is the progestational effect that allows safe and effective long-term therapy. Equilibrium between these 2 influences requires many months of treatment (8–15 months on 100 mg/day and 15–20 months on 200 mg/day).

CPA has been approved for the treatment of prostate cancer, central precocious puberty, androgen-induced skin disorders (e.g. acne, seborrhea, idiopathic hirsutism, and alopecia), and reduction of the sex drive in sexual deviants. It is available as oral tablets (50 and 100 mg) and a depot formulation for intra-muscular (IM) injection (100 mg/mL) in many countries. It is available in the United States only in a low-dosage form, in a combination product with ethinyl estradiol.

Most of the clinical data regarding its use in abnormal sexual behaviors have been generated using the oral formulation (usual regimen, 50–200 mg/day; maximum, 600 mg/day). The IM formulation is usually administered as 300–600 mg every 1 or 2 weeks for this indication. During use for its approved indications, general malaise is a common occurrence early in therapy; flushes, dizziness, depression, venous thromboembolism (VTE), decreased pubic/facial hair growth, psychotic reactions, and increased (more common) or decreased body weight have also been reported. Gynecomastia, which occurs in about 20% of patients, can be temporary or permanent, unilateral or bilateral. Serious hepatotoxicity is not a common finding with CPA. Although large doses of this agent can produce hepatomas in rats, no evidence exists that the same happens in humans. Flutamide and CPA may be cross-reactive in terms of hepatotoxicity risk. The most serious potential adverse events of CPA are suppression of the hypothalamic-pituitary-adrenal axis and a reduction in the adrenal response to stress. Early data were conflicting, but more recent information is reassuring concerning the adrenal safety of this agent.

In some countries, the oral form is the only form available and treatment observance

may be erratic. In fact, using this formulation, T levels are not systematically decreased and measurements of plasma levels of CPA are not available in many countries. Poor treatment compliance is a major concern with oral CPA. On the other hand, compared with the oral formulation, injectable CPA (via IM depot injection) shows a lower tolerability, in terms of local pain (at the injection site), joint/muscle pain, headache, sleep disturbances, and nausea.

Side effects are dose related and careful monitoring of CPA dosage should decrease side effects and, in some cases, would allow non-deviant sexual behavior. The use of CPA has to be managed carefully medically, via physical examination, especially for the unwanted effects of feminization.

TIPS & TRICKS

Clinical assessment for subjects treated with CPA:

- Before treatment, check:
 - T, FSH, LH, and prolactin plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, calcium and phosphate blood levels, kidney function, blood pressure, weight, bone mineral density.
- Informed consent must be obtained.
- During CPA treatment, evaluate:
 - every 1–3 months: depression, emotional disturbances;
 - every month for 3 months and then every 3–6 months: biochemical monitoring of liver function;
 - every 6 months: prolactin, glucose blood levels, blood cell count, calcium and phosphate blood levels, blood pressure, weight;
 - every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

CPA treatment must not be used in cases of:

- non-consent
- puberty not completed, especially when bone growth is not achieved
- hepatocellular disease, liver carcinoma
- diabetes mellitus
- severe hypertension
- carcinoma, except prostate carcinoma
- pregnancy and breast feeding
- previous thromboembolic disease
- cardiac and adrenal disease
- severe depressive disorder, psychosis
- tuberculosis
- chachessia
- epilepsy
- drepanocytosis

Medroxyprogesterone Acetate (MPA)

Compared with CPA, MPA is less potent than an antiandrogen and progestogen, and relatively more progestogenic than antiandrogenic (as opposed to the "balanced" effects with CPA). MPA exerts negative feedback on the hypothalamo-pituitary axis, resulting in an inhibition of gonadotropin secretion and hence T production. A complete ablation of the latter is reached usually within 1–2 weeks after starting therapy. Moreover, MPA also induces the testosterone-α-reductase, which accelerates T metabolism, and reduces plasma T by enhancing its clearance.

MPA has been approved for the treatment of menorrhagia, secondary amenorrhea, and mild to moderate endometriosis, female contraception, catamenial epilepsy therapy; and the treatment of prostate, breast, and advanced endometrial/renal cancers.

MPA is available in some countries as oral tablets (2.5, 5, and 10 mg) and l50- and 400-mg/mL suspensions for IM injection. Although the oral route of MPA can be used (usual regimen, 100–500 mg/day), erratic oral bioavailability (within and between products and within and between subjects) has made

the IM formulation preferable. The majority of clinical trial data regarding MPA use in abnormal sexual behaviors has been generated using the IM formulation (usual regimen, 100–1,000 mg weekly).

MPA adverse events included reduced bone mineral density (virtually 100%), excessive weight gain (18%), headache (9%), malaise (5%), dyspepsia (5%), VTE (<1%), muscle cramps (<1%), gallstones (<1%), and diabetes mellitus (<1%). A recent study has reported the balanced effects on D-dimer levels and activated partial thromboplastin time values (which have opposing effects on VTE risk) in a sample of women using MPA. This latter result suggests that the potential risk of VTE with MPA may be lower than once thought.

MPA was the first drug studied in the treatment of paraphilias. Unfortunately, most studies were not controlled and some biases were observed. Moreover, considering the severe side effects observed with MPA, the benefit/ risk ratio seems to be unfavorable and, therefore, its use has been limited.

Nevertheless, if clinicians decide to initiate MPA therapy for a paraphilia, they must take into consideration its toxicity potential and, in an attempt to prevent or ameliorate adverse events, the dose may be lowered, at the cost of reduced therapeutic efficacy. The use of MPA has to be carefully managed medically, via physical examination, especially for the effects of feminization.

☆ TIPS & TRICKS

Clinical assessment for subjects treated with MPA:

- Before treatment, check:
 T, FSH, LH and prolactin plasma levels, hepatocellular blood tests, blood cell count, electrocardiogram, fasting glucose blood level, calcium and phosphate blood levels, kidney function, blood pressure, weight, bone mineral density.
- Informed consent must be obtained.
- During MPA treatment, evaluate:
 – every 1–3 months: depression, emotional disturbances;
 – every 6 months: glucose blood levels, blood pressure, weight;
 – every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

MPA treatment must not be used in case of:

- non-consent
- puberty not completed, especially when bone growth is not achieved
- adrenal disease
- pregnancy and breast feeding
- severe hypertension
- previous thromboembolic disease
- breast and uterine diseases
- diabetes mellitus
- severe depressive disorder
- allergy to MPA
- active pituitary disease

GnRH analogs

GnRH analogs are relatively new drugs approved in many countries for a variety of pediatric, obstetric, gynecological, and oncological disorders, such as central precocious puberty, endometriosis, uterine fibromyomas, female infertility (*in vitro* fertilization), breast cancer (in pre-menopausal women), and advanced prostate cancer. Recently, they have also been used in Gender Identity Disorder subjects.

GnRH analogs produce a complete "chemical castration," with hypoandrogenism as the only clinical effect. Their biological effects depend on their duration of use. Initially, the release of LH and FSH is stimulated, leading to elevations in sex hormone blood concentrations ("flare-up"). Continued use results in a suppression on account of the depletion and desensitizing of

the gonadotrope hypophyse cells. The result is reduced LH and FSH secretion and thus reduced sex hormone production until castrated levels within 2–4 weeks. Because of these time-dependent effects of the LHRH agonists, concurrent use of a pure antiandrogen (flutamide or one of its congeners) is recommended during the initial 1 or 2 months of LHRH agonist use. Using an oral antiandrogen counteracts the "flare-up" of the androgen-dependent response that occurs with the initial surge in serum androgen concentrations early during LHRH agonist therapy. Oral antiandrogen therapy can be stopped once this phase is over.

Three analogs of the gonadotrophin-releasing hormone are available:

1) Triptorelin is a synthetic decapeptide agonist, analog of the gonadotropin-releasing hormone (GnRH). It was recently approved in Europe for the reversible decrease in plasma T to castration levels, in order to reduce the drive in sexual deviations of adult men. It was developed as monthly or depot formulation.
2) Leuprolide is a synthetic analog of GnRH; it was developed as daily IM or depot injections.
3) Gasorelin is also a synthetic analog of GnRH. It was developed as daily IM or depot injections.

Adverse events include decreased testicular volume (4–20%), decreased pubic/facial hair growth (2–23 %), and vasomotor instability (hot flashes; 56–100%). Other adverse events include fatigue and malaise (6–18% each), weight gain (2–13%), gynecomastia (2–7%), and injection-site reactions (induration, burning, redness, itching, bruising, and pain). Most concerning is the reduction in bone mineral density that occurs almost universally due to androgen ablation.

Forty percent of normal controls reported reduction in sexual desire with GnRH treatment. In addition, GnRH containing neurons project into pituitary and extrapituitary sites, such as the olfactory bulb or the amygdala. At these latter sites, GnRH is believed to act as a neuromodulator and, through this action, may also be involved in sexual behavior. Thus, GnRH analogs, by inducing castrate T levels, progressively led to and maintained the inhibition of the fundamental elements of male sexuality: sexual fantasies, desire, and interest in sexual activities, resulting in either a dramatic decrease or an abolishment of the sexually deviant behavior.

The duration of treatment necessary to achieve a complete disappearance of deviant sexual behavior and the conditions of treatment interruption remain open.

Efficacy was maintained for years as long as the antiandrogen treatment was maintained. Despite there being no controlled studies and some biases were observed, the efficacy reported in these open studies was very high and, in most cases, subjects were previously treated with psychotherapy or other antiandrogens without efficacy.

The World Federation of Society of Biological Psychiatry (WFSBP) guidelines suggest that GnRH agonist treatments should be used after other alternatives have been ruled out or when there is a high risk of sexual violence and underline that GnRH analog treatment probably constitutes the most promising treatment for sex offenders with a high risk of sexual violence, such as pedophiles or serial rapists.

☆ TIPS & TRICKS

Clinical assessment for subjects treated with Long Acting GnRH analogs:

- Before treatment, check:
 T, FSH, LH, electrocardiogram, fasting glucose blood level, blood pressure, weight, calcium and phosphate blood levels, kidney function, bone mineral density (in case of personal or familiar osteoporosis risk or in patient over 50 years old).

- Informed consent must be obtained.
- During Long Acting GnRH treatment, evaluate:
 - every 1–3 months: depression, emotional disturbances
 - every 6 months: glucose blood levels, lipid profile, blood cells count, calcium and phosphate blood levels, blood pressure, weight
 - every year, in case of increased osteoporosis risk: bone mineral density.

CAUTION

GnRH treatment must not be used in case of:

- non-consent
- puberty not completed especially when bone growth is not achieved
- pregnancy and breast feeding
- severe hypertension
- severe cardiac or renal disease
- severe osteoporosis, especially in case of previous fractures
- severe depressive disorder
- allergy to GnRH
- active pituitary disease

EVIDENCE AT A GLANCE

MPA and CPA treatment vs.long-acting GnRH analogs

Efficacy:

- Antiandrogen or GnRH analogs significantly reduce the intensity and the frequency of sexual arousal, but do not change the content of paraphilias.
- Long-acting GnRH analogs are more potent than CPA or MPA in reducing T levels, more dramatically and more consistently.

Side effects:

- MPA and CPA are associated with a high percentage of side effects, which have limited their use considerably.
- Long-acting GnRH induce fewer side effects (except for those related to hypoandrogenism).

Patient's compliance:

- Uncontrolled breaks in the therapy are often observed with CPA or MPA treatments.
- Long-acting GnRH analogs may be administrated parenterally once every 1–3 months, producing less variable results in the treatment of paraphilic behavior than CPA and MPA.

Algorithm of treatment of paraphilias

A treatment program should start with supportive psychotherapy and, in most cases, cognitive-behavioral therapy. In all cases, treatment of comorbidities is necessary, if there are any (Level 1). In case of psychiatric comorbidities, adequate pharmacological treatment, such as benzodiazepines, anti-psychotics, SSRIs, or specific types of psycho-therapies, must be used.

In mild cases with strong deviant fantasies or impulses and any risk for sexual offenses, psychotherapy in combination with SSRI treatment should be considered, especially if the paraphilic patient shows additional symptoms, such as anxiety, social phobia, depression, severe feelings of guilt, obsession, or personality disorders, and if the paraphilia is at low risk of sexual offense (Level 2).

If there is insufficient improvement and a moderate-to-high risk of "hands-on" offenses, low doses of antiandrogens, preferentially in combination with SSRIs, should be given. Side effects are dose related, so a careful titration could minimize them and may allow patients to maintain appropriate sexual behavior while eliminating deviant behavior (Level 3).

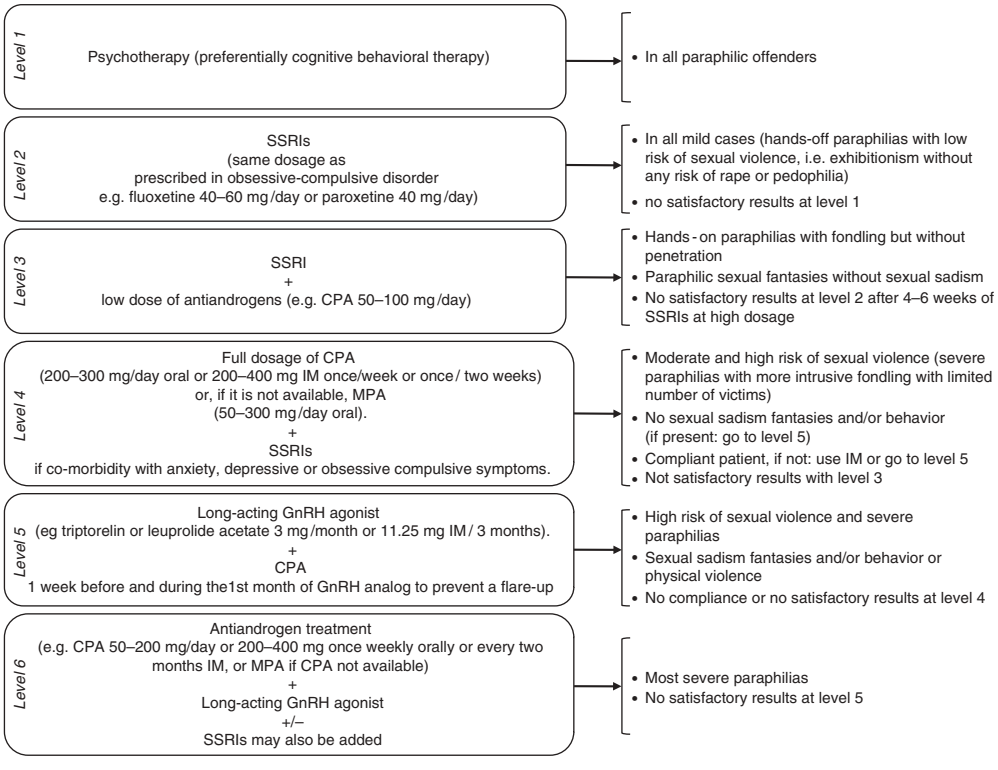


Figure 8.1. Treatment algorithm of paraphilias, modified from Thibaut F *et al*. The World Federation of Society of biological Psychiatry (WFSBP) Guidelines for the biological treatment of paraphilias. Altered from original source - *The Journal of Biological Psychiatry.* 11:604–55. 2011. SSRIs, Selective serotonin reuptake inhibitors, CPA, Cyproterone acetate; MPA, Medroxyprogesterone Acetate; GnRH, gonadotropin-releasing hormone; IM, intramuscolar.

Full dosage of CPA (or, if it is not available, MPA) should be added to SSRI treatment in subjects with a moderate to high risk of sexual offense (severe paraphilias with more intrusive fondling with limited number of victims), considering the intramuscular application in non-compliant patients (Level 4).

In case of high risk of sexual offense and severe paraphilias, sexual sadism fantasies and/or behavior or physical violence and no compliance or no satisfactory results at Level 4, use of GnRH agonist could be justifiable and useful (Level 5).

Finally, in most severe paraphilias, a combination of antiandrogens, GnRH agonist, and SSRI must be considered (Level 6).

In case of serious side effects (VTE or severe liver dysfunction), CPA or MPA treatment must be replaced with GnRH analogs.

For a summary of the treatment algorithm, see Figure 8.1.

Treatment duration

Paraphilia is a chronic disorder and sexual orientation will not change during the treatment.

In case of mild paraphilia, a treatment of at least 2 years might be used, after which, in case of treatment interruption, the patient must be carefully followed up. In case of recurrence of paraphilic sexual fantasies, treatment must be restarted.

For severe paraphilia with a high risk of sexual violence, a minimal duration of treatment of 3–5 years is necessary. In these patients in particular, hormonal treatment must not be stopped abruptly.

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9

Sexual Aspects of Klinefelter's Syndrome and other Sex-Chromosome Disorders

Linda Vignozzi, Annamaria Morelli, and Mario Maggi

University of Florence, Florence, Italy

Introduction

Physiopathology

In 1942, Harry Klinefelter and colleagues described a male syndrome characterized by tall stature with eunochoidal body proportions, small testes, azospermia, gynecomastia, and increased urinary excretion of FSH. Fifteen years later, it was reported that patients with Klinefelter's syndrome (KS) had sex chromatin material in epithelial cells similar to normal females; and then in 1959, Jacobs and Strong (1959) found that a chromatin-positive patient with KS had a 47,XXY karyotype.

The XXY karyotype occurs in 1 in 500 live male births and is the most common type of human chromosome anomaly. The prevalence of the syndrome rises to 3–4% among infertile males and to 10–12% in azoospermic subjects. About 90% of cases are due to the 47,XXY karyotype, whereas the 46,XY/47,XXY mosaicism and, less frequently, higher grade X aneuploidies (48,XXXY, 49,XXXXY) can be found in the remaining 10% of cases. Even though most human trisomies are due to errors at maternal meiosis I, the origin of the extra X chromosome in KS is due to a phenomenon of non-disjunction, which can be either maternal or paternal, with the same probability. The maternal extra X chromosome can derive by a meiosis I, a meiosis II error, or a mitotic error in the early developing zygote, whereas the paternal X chromosome can derive only by a meiosis I error. In contrast with some studies suggesting the influence of the parents' advanced age in the pathogenesis of the syndrome, the mean ages of mothers and fathers at birth of a large group of Klinefelter subjects were not found significantly different from those of control subjects undergoing evaluation for infertility/hypogonadism and with normal karyotype.

SCIENCE REVISITED

The most frequent karyotype is 47,XXY (80–90% of cases), the other cases present supranumerous X chromosomes (48,XXXY, 49,XXXXY) or mosaicism with a mixture of normal and 47,XXY cells (or mixtures of 47,XXY and other karyotypes, such as 47,XXY/48,XXXY). The severity of the phenotype in KS is directly correlated to the number of supernumerary X chromosomes, suggesting an effect

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related to the genic dosage. It has been estimated that each extra X is associated with a decreased intelligence quotient (IQ), with language most affected. Mosaicism generally results in a milder phenotype.

Clinical presentation

Unlike chromosomal abnormalities on autosomes, the 47,XXY karyotype leads to a very broad clinical spectrum of the phenotype of adult Klinefelter subjects, which ranges from clinically overt hypogonadism to normal virilization. This mildness of clinical presentation is probably due to inactivation of most genes on the supernumerary X chromosome. However, there are genes that lie in the pseudo-autosomal region on the X chromosome that have homologs on the Y chromosome, and tend to escape the silencing during the supernumerary X chromosome inactivation process. Nowadays, it is well recognized that Klinefelter's original description of the syndrome is too limiting, because it represents a broad spectrum of phenotypes, professions, incomes, and socio-economic statuses. Due to the variability of the phenotype and also to the fact that the main symptoms of the syndrome (androgen deficiency, infertility) are in the reproductive domain, approximately two-thirds of Klinefelter subjects are not diagnosed during their life, as recently demonstrated by the National Danish Cytogenetic Registry Study showing a prenatal and adult prevalence of the 47,XXY karyotype of 153 and 40 per 100,000 males, respectively.

It has been recently reported that, in adulthood, most men with KS will visit their physicians because of infertility and/or sexual dysfunction. The issue related to infertility in KS have been significantly improved during the last 10 years by the advent of combined testicular sperm extraction (TESE) and assisted reproductive technologies (ART). This topic has been extensively covered by several recent reviews. In contrast, the issue related to KS sexual function and dysfunction is less studied.

Sexual differentiation and behavior is a multi-step process, which begins early on in foetal life, according to the sex difference of the chromosomes established at conception (chromosomal sex). In fact, chromosomal sex determines gonadal production of androgens and the Müllerian inhibiting hormone (gonadal sex), which finally dictate the appearance of external and internal genitalia (anatomic or phenotypic sex). Sex differences between male and female brain organization and cognitive processes occur either under the control of a complex series of genetic (sex determining region Y (SRY); silencing of X chromosome; several epigenetic events), but also hormonal (gonadal steroid hormones and their receptors) events. SRY is the testis-determining gene, which causes the embryonic undifferentiated gonad to develop into a testis rather than an ovary. This event represents the primary developmental decision that will determine whether an individual will be and behave as a male or a female. Indeed, the embryonic testis secretes sex steroids, particularly the surge of testosterone during the early period of development (an epoch of extreme sensitivity to the environment) that enters the brain, causing a masculine pattern of brain development and behavior. Sexual behavior is controlled by a set of brain regions that do not operate independently, but function against a background in which genetic and hormonal factors are crucial. In particular, perinatal testosterone surges are critical to masculinize such brain regions.

In Klinefelter patients, no indisputable hypoandrogenism has been observed, both in the perinatal period and infancy. When testosterone was investigated in amniotic fluid obtained at prenatal diagnosis between 16 and 20 weeks of gestation from 20 XXY fetuses and from XY controls of the same gestational age, no significant difference was evident. In a very limited number of KS subjects, cord blood testosterone at birth was reported not to differ from that observed in control infants. In the neonatal period, the

activation of the pituitary-gonadal axis occurs at 2–3 months of age (the so-called "mini-puberty"). This has been also reported in 18 Klinefelter infants, but mean testosterone levels were lower than in 215 healthy boys, thus suggesting an early impairment of Leydig cell function. In contrast, Aksglaede and colleagues found high normal testosterone level in 10 Klinefelter infants, when compared to healthy controls.

Data from longitudinal follow-up study of 14 pre-pubertal and pubertal XXY boys demonstrated that pre-pubertal 47,XXY boys are characterized by normal serum levels of testosterone and gonadotropins. At puberty, after an initial normal adolescent increase, serum testosterone concentrations plateau and remain subsequently within the low-normal range throughout the pubertal age, allowing a satisfactory development of secondary sexual characteristics.

☆ TIPS & TRICKS

Examining a patient for sexual problems can be an opportunity for the diagnosis of KS. In adulthood, most men with KS will visit their physicians because of infertility and/or sexual dysfunction. Sexual symptoms eventually present in KS have been demonstrated to be not specifically associated with the syndrome but to the underlying hypogonadal state.

☆ TIPS & TRICKS

In Klinefelter patients, no indisputable hypoandrogenism has been observed, both in the perinatal period and infancy. At puberty, after an initial normal adolescent increase, serum testosterone concentrations plateau and remain subsequently within the low-normal range throughout the pubertal age, allowing a satisfactory development of secondary sexual characteristics.

Emotional brain in KS patients

Sexual behavior is controlled by a set of complex neuroanatomical and neurochemical pathways, which are commonly referred to as the emotional brain. The set of brain regions that are critically linked to emotion includes both some subcortical regions (namely the amygdala, the nucleus accumbens, and the hypothalamus), and the major prefrontal cortex sub-regions (namely orbitofrontal cortex, the anterior cyngulate cortex, and the ventromedial prefrontal cortex). Among these, the amygdala occupies a very geometric center and activates in response to sexual stimuli. Previous studies in rats, sheep, primates, and humans have demonstrated a positive correlation between amygdala volume and sexual functioning.

Interestingly, a volume reduction in left temporal gray matter, and a specific amygdala reduction, were demonstrated in adult KS patients in MRI studies based on manual delineation of regions of interest (ROIs). In a larger structural MRI study, using automated method for voxel/regional parcellation and volumetric analyses, Shen *et al*. observed pronounced gray matter density reductions of the right amygdala, left insula, and cingulated gyrus in 34 KS patients compared to 62 healthy matched controls. A decreased cortical thickness in the temporal regions has been reported to be present also in child KS patients. Taken together, findings from MRI studies show structural abnormalities of brain regions that form part of a neural network subserving social cognition and emotion. However, no clinical data on sexual function are available in these studies.

Recently it has been proposed that in 47,XXY men, reduced activation in the amygdala is responsible for the less accurate perception of socio-emotional cues and impairment in emotional prosody in comparison to the general population. Interestingly, amygdala, the central hub in the emotional brain, is recognized to be subject to a high degree of androgen-dependent plasticity,

even in the adulthood, as will be discussed in the next paragraph.

The reduced size of the amygdala, as well as of the left temporal lobe in subjects with KS, was found to be at least partly due to androgen deficiency, as it was less apparent in testosterone-replaced KS subjects. In particular, in a small study involving 10 subjects with KS, variation in brain morphology associated with supernumerary X chromosome was not present in the subgroup of KS subjects that had received testosterone supplementation since puberty.

This suggests that the human brain, also in Klinefelter syndrome, retains plasticity to be continually modified by externally supplemented hormones, as testosterone. Indeed, androgen receptor are highly expressed in the male brain, and are particularly present in neurons constituting the neural rewarding circuits mediating sexual behaviors, such as the amygdala, the nucleus accumbens, the stria terminalis, the medial preoptic area, and the ventromedial.

Recent observations suggested that the "morphogenic and organizing" action of testosterone on the human brain is not limited to the foetal period (Chapter 1) but is also present in young adulthood. Neufang and colleagues demonstrated that amygdala and hyppocampal volumes varied as a function of Tanner stages and were associated with circulating testosterone levels during male puberty. Indeed, during puberty, neural connections between amygdala and frontal areas are strengthened, supporting a role for postpubertal hormonal changes in the maturation and refinement of the limbic circuitry. Frontal brain activity increases during puberty and this is assumed to contribute to advances in cognitive processes (abstract reasoning skills and attentional capacities), which is a definite component of sexual maturation.

These data support the view that the crucial regions of the emotional brain are extremely sensitive to testosterone, also during adulthood. In agreement, it has been demonstrated that testosterone level was positively associated with men's attention to socially relevant stimuli, and more recently with men's interest in sexual stimuli, evaluated both as self-regulated viewing times for pornographic images and as reported attraction to femininity in women's faces. Taken together, these data suggest that endogenous testosterone level may modulate men's interest in sexual stimuli. In adult males, testosterone influenced reproduction and sexuality, whetting sexual desire but also regulating all the other steps of sexual response, namely sexual excitation and orgasm/ejaculation. Nowadays it is well known that one of the main physiological functions of testosterone is to tune up erection with sexual desire, finalizing erection to emotional processing.

TIPS & TRICKS

Testosterone exerts a morphogenetic and trophic effect on a well-mapped set of brain regions dedicated to emotional processing and sexual behavior. This testosterone-dependent morphologic plasticity, that have traditionally been thought to characterize foetal and neonatal life, might be operative also in adulthood, as also demonstrated in the study of KS patients.

SCIENCE REVISITED

Findings from MRI studies show structural abnormalities of brain regions that form part of a neural network sub-serving social cognition and emotion in KS patients. Variation in brain morphology associated with supernumerary X chromosome was not present in the subgroup of KS subjects that had received testosterone supplementation since puberty.

KS and sexual dysfunction

It is generally reported that in KS, low libido and erectile dysfunction are present; however, only few studies have specifically investigated this point.

Yoshida and colleagues compared the sexual features of 40 KS patients to 40 non-azospermic infertile 46,XY patients, by using a questionnaire on sexual function. Among their sample, 90% of KS patients showed normal and 10% a slightly decreased sexual desire, while 97.5% had a normal erection during the whole duration of intercourse, while the remaining demonstrated a normal erection with shrinkage after entering into the vagina. Orgasm was normal in 80% of KS patients, while it was slightly decreased in about 17%, and significantly decreased in about 2%. However, there was not a significant difference in the frequency of sexual function disturbances between the patients with KS and the control group. On the contrary, the mean frequency of intercourse in KS patients was significantly higher than in the control group. Another study compared coital activity in groups of married men with KS and in men with a varicocele investigated for marital infertility. Frequency of intercourse in both groups did not significantly differ. One of the main limitations of these studies is that both have been performed in a population sample of subjects among whom the chief complaint was of infertility and not sexual dysfunction.

Corona and colleagues analyzed the prevalence and the specific sexual correlates of KS in a consecutive series of male adult patients attending an outpatient clinic for sexual problems. Interestingly, among a consecutive series of 1,386 patients, a relatively higher prevalence (1.7%) of KS was observed, than that reported in the general population. This indicates that sexual dysfunction is a common feature of KS and that clinical settings for the treatment of sexual problems are a convenient site for the diagnosis of KS. In this population, as expected, KS was associated with lower level of education, a more frequent history of cryptorchidism, poorer pubertal progression, a less often performed military service, elevated triglycerides, and a higher risk of gynecomastia. When sexual parameters were evaluated, 22.7% of KS patients reported severe ED (an erection not sufficient for penetration in >75% of cases), 60.9% hypoactive sexual desire (HSD), 9.5% premature ejaculation, and 9.5% delayed ejaculation. However, adjusting for age, in a multiple logistic regression model, only a higher risk for HSD continued to be observed in KS subjects. The frequency of sexual intercourse and masturbation was not significantly different, while a higher risk of reduced ejaculate volume, and a later referral to an andrology service were observed in KS patients when compared to the control. In addition, KS showed, even after adjustment for age, a higher prevalence of overt primary hypogonadism. When KS patients were compared to testosterone matched control subjects, all the above-mentioned sexual and non-sexual problems were no longer associated with the syndrome, and only the typical features of KS (namely gynecomastia, tall stature, higher frequency of cryptorchidism, history of poorer pubertal progression, lower level of education) retained association with the syndrome. In conclusion, this case-control study indicated that hypoactive sexual desire, eventually present in KS subjects, is more related to the testosterone deficiency than to the genetic abnormality. Accordingly, in a small placebo control study on the effect of TRT in subjects with KS, it has been reported that an increase in sexual interest was observed during TRT.

KS, metabolic syndrome and sexual dysfunction

Metabolic syndrome (MetS), diabetes, and cardiovascular disease (CV) are often associated with KS. The association between hypogonadism, MetS, and CV has also been emerging, both in subjects with and without

sexual dysfunction. In addition, prospective studies have clearly demonstrated that low T at baseline could predict the development of diabetes mellitus and MetS, and vice-versa. Although additional data are worthwhile, most cross-sectional studies have reported a direct correlation between testosterone concentrations and more favorable CV risk factor profiles, including higher HDL and lower triglyceride concentration, blood glucose, blood pressure, and body mass index. In addition, both clinical and animal evidence shows that T exerts a favorable effect upon vascular reactivity, inflammation, cytokine production, and adhesion molecule expressions, as well as on serum lipid concentration and haemostatic factors. The presence of hypogonadism in subjects with sexual dysfunction can further worsen the problem, adding typical symptoms such as hypoactive sexual desire and mood disturbances. Waist circumference and hypertriglyceridemia have been considered the most important MetS determinants of hypogonadism in subjects with sexual dysfunction. As stated above, KS patients demonstrated a higher prevalence of erectile dysfunction and hyper-triglyceridaemia, when compared to patients without KS. Although the cross-sectional data available at the moment cannot allow any final conclusions to be drawn, Corona's study suggests that KS-associated hypogonadism might play the major role in the pathogenetic mechanism underlying KS-associated sexual dysfunction and MetS. In fact, the association between hypertriglyceridaemia and ED disappeared after adjustment for testosterone levels.

In conclusion, studies reviewed indicate that sexual features present in KS are not specifically associated with the syndrome but are more probably related to underlying hypogonadism. Hypogonadism, more than chromosomal abnormality, could underlie alterations in the emotional brain observed in KS patients. Hypogonadism also underpins the higher risk of hypertriglyceridaemia and sexual dysfunction observed in KS.

It can be also speculated that testosterone replacement therapy could produce an improvement of KS-associated increased risk of MetS and CV, besides the improvement of sexual function. However, further longitudinal studies are advisable in order to better clarify these points.

CAUTION

Remember that hypogonadism, more than chromosomal abnormality, could underlie alterations observed in KS patients, including sexual dysfunctions and MetS.

CAUTION

It can be speculated that testosterone replacement therapy could improve KS-associated increased risk of MetS and CV, besides the improvement of sexual function, as well as in non-KS hypogonadal patients.

The XX male syndrome

A clinical entity similar to KS is the so-called 46,XX male syndrome. 46,XX male sex reversal syndrome is also known as de la Chapelle syndrome, which was first reported by de la Chapelle *et al*. in the 1964. 46,XX male sex reversal syndrome is extremely rare, the incidence rate is about 1:20,000–25,000. This karyotype is associated with a very broad sprectum of clinical presentation: normal XX males, males with genital ambiguity, and true hermaphrodites. The normal male phenotype is the most frequent and in 90% of these patients, Y chromosome sequences are usually located on the distal tip of the short arm of the paternal X chromosome. In 10% of the XX males, testicular differentiation occurs in the absence of detectable Y sequences. These findings supports the theory that the SRY gene does not function alone in the determination of the male phenotype, but

that disruption of an unidentified autosomal or X-linked sex-determining gene may interact in the sex-determining cascade. In a recent study, the comparison of 11 SRY-positive 46,XX males and 101 Klinefelter subjects reported that 46,XX males are also hypogonadal and infertile, with small testes, a mean lower height (–13.4 cm) and weight (–12 kg), and a higher incidence of maldescended testes. No other significant phenotypic and biochemical differences with Klinefelter subjects were found, except extremely skewed androgen receptor allele inactivation ratios, with no preference toward the short and/or long AR allele. While the clinical symptoms of patients often show some degree of heterogeneity, usually the development of genitalia is normal and masculinity signs are obvious in SRY gene-positive patients. In a recent case report of a non-hypogoandal 46,XX male sex reversal subject, no abnormality in the development of penis and sexual function has been described.

☆ TIPS & TRICKS

A clinical entity similar to KS is the so-called 46,XX male syndrome: a sex reversal syndrome also known as de la Chapelle syndrome. In non-hypogonadal subjects, no abnormality in the development of penis and sexual function has been described.

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10

Sexual Counterpart of Hormonal Male Contraception

Maria Cristina Meriggiola, Antonietta Costantino, and Silvia Cerpolini

University of Bologna, Bologna, Italy

Introduction

Among all the experimental approaches tested so far for male contraception, hormonal methods seem to be the most promising in terms of efficacy and safety and the closest to the market. Although a final formulation has not been developed, progestin-testosterone combinations seem to represent valid regimens to induce profound sperm suppression and consequently, probably, to achieve good protection against pregnancy.

The effects of hormonal combinations on human sexuality are the result of a complex interaction between physical and biochemical changes, possibly induced by hormonal combinations and cognitive, cultural, and social factors (Table 10.1).

The hormonal approach to male contraception: history and state of the art

Mechanism of action of hormonal male contraception

The hormonal approach to male contraception is based on the reversible suppression of gonadotropins leading to reversible suppression of the spermatogenic process. Qualitatively and quantitatively normal spermatogenesis requires action of both gonadotropins, since either luteinizing hormone (LH), intra-testicular testosterone or follicle-stimulating hormone (FSH) alone can maintain some level of sperm production. Therefore, to suppress spermatogenesis, hormone administration must suppress both gonadotropins and intra-testicular testosterone concentrations. In this way, a block of both exocrine and endocrine testicular function (sperm and testosterone production) is achieved. For this reason, any hormonal contraceptive regimen has to include physiological testosterone replacement to maintain androgen dependent physiological functions and to prevent symptoms and consequence of hypogonadism. Spermatogenesis is arrested at the spermatogonial level and primordial germ cells do not appear to be damaged. This guarantees the most important characteristic of this method of contraception, namely full reversibility. After stopping hormone administration, gonadotropin secretion recovers, resulting in a complete resumption of Leydig cell function

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Table 10.1. Selected most promising hormonal male contraceptive regimens under development

Treatment	Authors and year	Men achieving sperm concentration ≤1 M/mL	Time to efficacy	Side effects		
		% (n. over total)	weeks	metabolic	mood/sex	other effects
TU 1,000 or 500 mg/4 wks	Gu Y *et al.*, 2009	95 (855/898)	≈15	**Increase**: Body weight; Blood pressure and Hb. **Decrease**: Tot-chol, HDL and LDL	**Increase**: Libido. Mood and behavior changes	Acne; facial swelling, and skin rashes; fear; occasional tenderness and discomfort at the injetion site; severe coughing, and low fever after injection
NETE 200 mg/6 wks + **TU** 1,000 mg/6 wks	Kamischke A *et al.*, 2002	93 (13/14)	16	**Increase**: Body weight, RBC, Ht, Hb, Tot-chol. **Decrease**: HDL; alkaline phosphatase; platelets	**Increase**: aggressive behavior; number of weekly ejiaculations	Mild acne; nocturnal sweating; pain at the injection site; mamillary pain/induration
NETE 200 mg/8 wks + **TU** 1000 mg/8 wks	Meriggiola MC *et al.*, 2005	100 (10/10)	16	**Increase**: Body weight and lean body mass. **Decrease**: HDL	no changes	N/A
DMPA 300 mg/12 wks + **T-pellets** 800 mg/16 wks	Turner L *et al.*, 2003	100 (51/51)	≈12	**Increase**: Body weight and Hb	undefined changes of sexual function	lethargy; gynecomastia
DMPA 300 mg/12 wks + **T-gel** 100 mg/day	Page *et al.*, 2006	90 (19/21)	9	**Increase**: Body weight. **Decrease**: Tot-chol and HDL	N/A	mild acne and skin reactions

(*continued*)

Table 10.1. (cont'd)

Treatment	Authors and year	Men achieving sperm concentration ≤1 M/mL	Time to efficacy	Side effects		
		% (n. over total)	weeks	metabolic	mood/sex	other effects
ENG Implant (high and low dose) + **TU** 750 mg/10–12 wks or 1,000 mg/12 wks	Mommers E *et al.*, 2008	89 (310/349)	16	**Increase**: Body weight. **Decrease**: Tot-chol, LDL and HDL	**Increase**: Libido. Mood swings	Acne; gynecomastia; nocturnal sweating
ENG Implant + **TD** 400 mg/4 wks **TD** 400 mg/6 wks **TD** 600 mg/6 wks	Brady BM *et al.*, 2006	93 (31/33) 100 (40/40) 93 (33/35)	≈8 ≈12 ≈9	**Increase**: Body weight, Hb and Ht. **Decrease**: Tot-chol and HDL	no changes	N/A
CPA 20 mg/day + **TU** 1,000 mg/6 wks then **CPA** 20 mg/day + **TU** 1,000 mg/8 wks **CPA** 2 mg/day + **TU** 1,000 mg/8 wks **Placebo**/day + **TU** 1,000 mg/8 wks	Meriggiola MC *et al.*, 2003	100 (22/22)	12	**Decrease**: Tot-chol, HDL, Hb and Ht	no changes	pain and reaction at the injection site

N/A: not available.
0–1 Million/mL: sperm concentration threshold for efficacy.
Time to efficacy: time necessary to reach sperm concentration compatible with optimal pregnancy protection.

and sperm cell maturation. This characteristic of full reversibility provides hormonal male contraception with an important advantage over other currently available forms of contraception.

Efficacy

Effectiveness of contraceptive protection provided by hormone suppression of spermatogenesis has been proved in 2 large multi-center trials supported by the World Health Organization (WHO 1996). In these studies, weekly injections of 200 mg of testosterone enanthate (TE) were used as a prototype hormonal regimen and the effectiveness of azoospermia and various degrees of oligoospermia were tested. In these studies, the pregnancy rate was related to sperm concentration, so that zero pregnancies occurred among azoospermic subjects, 2 pregnancies among subjects with a sperm count suppressed below 1 million/mL, and 4 pregnancies among subjects with a sperm count suppressed below 3 million/mL. These results suggest that azoospermia or severe oligospermia (<1 million/mL) would be the ideal goal to be achieved with hormonal contraceptive regimens. However, the administration of TE 200 mg/week induced azoospermia in only approximately 60% of Caucasian men studied. Therefore, even if these studies confirmed the validity of the basic principles of hormonal male contraception, they did not offer a sufficiently effective method for use in the wider population. Moreover, some unfavorable effects caused by the supra-physiological serum testosterone levels achieved with the weekly injection of 200 mg of TE were reported, such as the decrease of HDL-cholesterol, acne, weight gain, and a few subjects reported minor mood changes. The recent development of new androgen formulations with more favorable pharmacokinetic and pharmacodinamic characteristics, to be used for treatment of early or late hypogonadism, has represented an important development also in the field of hormonal male contraception.

Recently, a reasonably large study was completed in China by Gu (2009), in which a total of 1,045 couples were enrolled and asked to use this regimen for pregnancy protection. A total of 855 participants entered into the efficacy phase and 733 participants completed monthly Testosterone Undecanoate (TU) treatment and follow-up. Authors showed that among the couples that completed the efficacy phase, the contraceptive failure rate was 1.1 per 100 men over the 24-month efficacy phase. The protection provided by these regimens was excellent, not only when compared with male condoms (2% for perfect use, 15% for typical use) or withdrawal, but also with female hormonal oral contraception.

Different combinations

To obtain a more profound suppression of gonadotropins, and thus spermatogenesis and improved contraceptive efficacy, progestogens have been combined with T. The rationale for combining androgens with progestins to suppress fertility in men is based on the synergic and additive effects that the 2 steroids have at the hypothalamus-pituitary level, resulting in more profound gonadotropins and sperm suppression compared to administration of each agent alone. This combination allows for dose adjustment in order to achieve maximum suppression and at the same time to avoid supra-physiological serum androgen levels, thus improving the safety of the regimen. Based on this rationale, various studies have been performed in the last decade in which depot medroxyprogesterone acetate (DMPA), levonorgestrel (LNG), desogestrel (DSG), cyproterone acetate (CPA), norethisterone enanthate (NETE), and etonogestrel (ENG) were added to different androgens. None of these trials have reported major adverse events that could deter continuation of the use of these hormonal combinations. Of course, the choice of progestin is very important and the use of progestins with appropriate biological and pharmacological properties

will increase the safety of these regimens for long-term use.

The most promising hormonal combinations in terms of efficacy, acceptability, and absence of adverse effects are: NETE + TU; DMPA + T pellet and gel; ENG + TU and TD; and CPA + TU. In particular, the combination NETE + TU is currently used in a multi-center efficacy trial supported by WHO.

CAUTION

- Please remember that hormonal contraception does not protect against sexually transmitted diseases (STD) and for this reason it should not be used for occasional sexual intercourses.
- Do not use hormonal contraception in cases of steroid related disease.
- Check for possible interactions with use of concomitant medication.

Acceptability of a hormonal male contraceptive

Despite some skepticism regarding the potential demand for new male methods of contraception, results of population-based studies of contraceptive preferences indicate that, globally, a high percentage of men approve of family planning and use some form of contraception themselves (Ringheim 1995). Limited research has been done on the features that could influence men's acceptance of hormonal contraceptive methods for their use. Some of the most important attributes that would make such a method highly acceptable include high level and rapid onset of effectiveness, with the most acceptable methods being more effective than those presently available; convenience, not coitus-dependent, easy to use, and does not interfere with a couple's daily routine; reversibility; none or limited actual or perceived side effects; long-term safety; low cost and favorable physical properties, including odor and comfort. However, acceptability is dependent not only on factors related to the method but also on the user's, or potential user's, personal preferences, characteristics, and situation.

A few large-scale surveys have been performed in different countries and results show a high potential level of acceptability of hormonal methods of male fertility regulation. An important study involving 9,000 men in 9 countries on 4 continents was conducted in 2002. The acceptability of a new method of contraception for men was good, with 55.1% expressing their willingness to use such a method of contraception. Those unwilling to consider a new method reported preferring the condom (67.8%) (Heinemann 2005) The acceptability of a new method for men showed high variability determined by cultural background and current contraceptive usage. A multi-center study to assess men's attitude to a novel hormonal contraceptive method was organized in Edinburgh, Shanghai, Hong Kong, and Cape Town, where questionnaire-based structured interviews were administered to men. The majority of men welcomed a new hormonal method of contraception, declaring that they would use a male contraceptive pill (44–83%) (Glasier 2010).

Most of the clinical trials involving different hormonal combinations and routes of administration have collected data on user and often on the user's partner's satisfaction during and after the trial. This data is not expected to be representative of likely acceptability of a method among the general population, because it represents a selected population of men who have chosen to participate in a trial on male contraception. On the other hand, data was collected from people who had actually tested the method and may thus be in a better position to give an opinion. Moreover, these trials were performed in a range of different cultural settings, thereby representing the view of a wide spectrum of population. In a study where American men received T-gel (100 mg daily) plus DMPA (300 mg every 3 months) for 24 weeks, the overall acceptability of the

contraceptive regimen was 50%, with 32% of subjects finding the method unsatisfactory. Forty-five percent of subjects indicated a willingness to use this regimen if it was available, but 42% indicated that they would not. In respect to their previous methods, 40% of subjects found the regimen preferable, while 42% did not. In a trial involving Chinese men who received a monthly TU injection, most considered the method good for women who do not want or cannot use a female method, but considered it inconvenient for men (Page 2008). In a study conducted in our clinic, men received injections of NETE plus TU at different intervals and we explored acceptability of the method using self administered questionnaires. Nine-two percent of participants agreed that men and women should share responsibility for contraception, even though only 38% of the men overall would assume full responsibility for contraception; 75% of the volunteers indicated that they would try a new male contraceptive if available, and 74% thought that the female partner would welcome the use of such a method. Questions on the acceptability of this specific hormonal contraceptive regimen were asked at the beginning and end of the treatment phase. At the beginning of the study, 75% of men in the treatment group indicated that they would use such an injectable hormonal method of contraception if it were commercially available, whereas at the end of the treatment phase, 66% of men expressed a willingness to use it. Those participants who responded that they would not use such a method, indicated that the injections were the major obstacle to its use (Meriggiola 2005).

To the best of our knowledge, there are only 2 previous studies concerning the female view-point. In the USA in the late 1960s, women attending a family planning clinic were interviewed and asked, "If there was a pill for men like the pill for women, who would you prefer to be responsible for contraception?" Seventy-two percent of women said they would prefer to be in control of contraception themselves, 16% preferred men to take responsibility, and 12% said that the responsibility of contraception should be shared. Later, in a randomized telephone survey of 1,005 Americans, more than 70% of subjects (men and women) said that men should play a greater role in the use of contraception. In the same study, 45% of women thought that men would take a male pill, fewer thought that they would use an injectable method or implants, and 36% doubted that a man would use a hormonal male method if available. More recently, a study conducted on women attending family planning clinics in different countries showed that over 70% of women in Scotland, South Africa, and China would be willing to rely on hormonal male contraception if it became available and only 2% declared that they would not trust their partner to use it. In all 4 centers, the majority of women said that the introduction of a new hormonal method of contraception for men would be a good idea and over 84% of women agreed that it would allow a more equal share of responsibility for contraception (Glasier 2010).

Effects of hormonal male contraception on sexuality

Despite progress in the development of effective hormonal male contraceptives, data on possible effects of these combinations on sexual life, mood, and behavior are confused and poor. Most of the studies on male contraception completed so far have tested prototype regimens, with a small number of participants and using different formulations. There are few studies in which sexual function and behavior during hormone intake for contraception in men have been investigated. To use a placebo control group during efficacy studies on contraception is unethical and some of the instruments used were often old and not always validated. As a consequence, the real impact of hormone contraception administration on male sexuality is still unknown.

Analyzing literature, we tried to summarize available data on the psychosexual life of participants treated with different formulations in trials on hormonal male contraception.

The effects of supra-physiological testosterone levels on sexual behavior, mood, well-being, and quality of life were studied in men receiving weekly injections of 200 mg of TE. An increased interest in sex during TE treatment as opposed to no effect in the placebo group was registered. No change was reported in sexual behavior, but enhanced sexual arousal and enjoyment and an increased bias for auditory sexual stimuli was reported in men treated with TE (Anderson 1992). In another study, authors reported a trend toward increased arousal and spontaneous erections during TE 200 mg/ weekly administration, but this did not reach statistical significance. Frequency of sexual intercourse, masturbation, kissing, and fondling did not change, nor was the subjects' satisfaction in their relationships affected by T administration in 20 weeks of 200 mg TE administration in the Bagatell study (Bagatell 1994). Some data suggest increased sexual desire and a higher quality of sex life during the efficacy phase compared to the recovery phase in volunteers using TE weekly injection as the sole method of contraception (O'Connor 2004).

When the dose of TE was decreased to 100 mg, there were no significant differences in frequency of sexual intercourse, desire, fantasies, masturbation, kissing, or morning erections between control and treatment periods (Meriggiola 1996).

These results suggest that sexual awareness and some aspects of sexual arousal can be increased when supra-physiological testosterone levels are induced. However, these changes are not reflected in modifications of overt sexual behavior, which in eugonadal men may be more determined by relationship, cultural, and social factors. This contrasts with hypogonadal men, in whom testosterone replacement clearly stimulates sexual behavior. There was no evidence to suggest an alteration in any of the mood states studied, in particular those associated with increased aggression.

The new T formulation of TU dissolved in castor oil induces lower T peaks and overall more stable T levels compared to the old short-acting formulations, and the effects on sexuality and behavior were negligible in almost all studies (Meriggiola 2005; 1996; Kamischke 2002). The Chinese formulation of TU dissolved in tea-seed oil has also a more favorable pharmacokinetic, and when administered at the dose of 500 or 1,000 mg/4 weekly, occasional self-reported changes in sexual desire, more commonly increased rather than decreased, and no changes in aggressive behavior and mood states were reported. When TU 1,000 mg was administered as a single dose in a double-blind placebo controlled study, in normal men, results showed that elevation of T to supra-physiological or high normal levels for 2–4 weeks had significant minor effects on mood but none on aggressive tendencies or other aspects of behavior, such as assertiveness, irritability, self-esteem, or sexual function (O'Connor 2004).

Preliminary studies on hormonal male contraception used progestins administered alone, without T. In these studies, as expected, subjects experienced side effects, including decreased sex drive, tiredness, and feelings of depression (Meriggiola 2003)

When androgen progestin regimens were tested, the dose of T could be reduced to avoid the raising of supra-physiological T levels. With these formulations, some differences were found, mainly related to the progestin used.

CPA is a synthetic progestin with anti-androgenic activity. When used in high doses with 100 mg of TE, a decrease in morning erections was reported by a small group of volunteers. At lower dosages (50, 25, and 12.5 mg/d), no significant difference in frequency of sexual intercourse, desire, fantasies, masturbation, kissing, or morning erections between control and treatment

groups was detected. Levels of aggressive behavior and mood states reported by both the subjects and their partners did not show any change. There was no change in the subject's satisfaction with their relationships during the treatment period, which lasted only 16 weeks (Meriggiola 1996; 2003).

The use of 19 non-derived progestins such as LNG and NETE at different doses, and with different T formulations, also did not induce any changes in mood ratings, individual well-being, or frequency of erections and sexual intercourse at any investigated point in time (Page 2008; Liu 2010).

In Kamischke's studies, when NETE was administered at different doses with TU 1,000 mg, 13 out of 40 volunteers complained of increased nocturnal sweating during treatment. Three volunteers complained of increased general sweating during treatment. Further adverse events possibly related to the medication were subjectively increased aggressive behavior (1 volunteer), pain at the injection site (1 volunteer), and short duration of erectile dysfunction (1 volunteer). All adverse events mentioned above, which were possibly related to the study medication, had disappeared at the end of the treatment period.

The third-generation progestin DSG, or its active metabolite ENG, were also used in combination with different androgen formulations (T pellets, 7α-methyl-nortestosterone (MENT) or Testosterone Decanoate (TD)) for male contraception. Even with this progestin, which retains lower androgen activity compared to the 19 non-derived progestins, no relevant effects on sexual function or mood could be consistently detected (Page 2008; Meriggiola 2003; Liu 2010). When the ENG was administered in combination with TU, adverse events such as acne, (night) sweating, mood changes, change in libido (28 of 38 men had increased libido), and weight gain were reported, more frequently in the active treatment groups compared with the placebo group (ENG + TU) (Mommers 2008). Even though, during the treatment phase, subjects reported side effects, namely increased sex drive, decreased sex drive, emotional liability, irritability, and tiredness, the authors concluded that these were transient in nature and unrelated to treatment groupings (DSG + T patches). Both injectable and gel DMPA at adequate doses did not induce consistently sexual symptoms when used with T. At the end of the treatment periods, DMPA tends to accumulate in the subcutaneous tissue from where it is slowly released. This induces a period of symptomatic androgen deficiency (lethargy, sexual dysfunction, and gynecomastia) in men, due to a delay in recovery of the hypothalamic-pituitary axis after discontinuation of treatment, probably due to the residual effects of the DMPA injection (Page 2008; Meriggiola 2003; Liu 2010).

Conclusion

In conclusion, the effects of hormones administered for contraceptive purposes on sexual function and behavior in men remain largely undetermined. Supra-physiological T levels induced by exogenous T administration in normal men induces an increase in some aspects of sexuality, without significant changes in sexual behavior or mood states. For this reason, and also to avoid metabolic effects, the mainstay of hormonal

☆ TIPS & TRICKS

Even if most contraceptives currently available are for women, new contraceptives for men are being studied. Among those under development, hormonal contraceptive regimens are the closest to widespread clinical application. New effective, safe, and reversible contraceptives for men will provide men with the possibility to share responsibilities in family planning. Information about effects on sexual function of the hormonal formulations under development is scant. Once definitive hormonal formulations have been defined, further research on this issue will be needed.

contraception in men is to maintain T levels within the normal range. With the development of formulations with more favorable PK, more stable T levels can be achieved and the effects on sexual aspects and mood due to fluctuating T levels have become negligible. Hormonal male contraception, like female, allows for the separation of sex from reproduction. This aspect will certainly have an influence on many aspects of male sexuality. The development of female hormonal contraception in the last 50 years has empowered women, allowing for a free and autodetermined sexuality, but at the same time has almost exclusively placed on them the burden of family planning. Once hormonal male contraception is widely used and entered into male culture, men will have the chance to share the responsibility and benefits of contraception. As a result of this, the couples' relationships and thus sexual life is expected to undergo further changes that are now difficult to forecast.

SCIENCE REVISITED

Development of hormonal regimens that maintain peripheral physiological testosterone levels allows for safe formulations in terms of metabolic and sexual effects. The development of hormonal combinations with physiological doses of androgen represents one of the most important aims in this field.

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